

# **Levothyroxine Tablet Products: A Review of Clinical & Quality Considerations**

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## Table of contents

1	Lay Summary .....	2
2	Introduction.....	4
2.1	Issue .....	4
2.2	Previous regulatory reviews .....	6
3	Clinical Review .....	7
3.1	Overview .....	7
3.2	Introduction .....	7
3.3	Is levothyroxine a Narrow Therapeutic Index drug?.....	7
3.4	Stability of levothyroxine over its shelf-life and its clinical consequences.....	8
3.5	Issues around bioequivalence of levothyroxine products.....	9
3.6	Discussion and Conclusions.....	10
4	Pharmaceutical Quality Aspects .....	12
4.1	Overview .....	12
4.2	Bioavailability and Bioequivalence: Solubility, Permeability and Dissolution Rate... 12	
4.2.1	Background .....	12
4.2.2	Determination of solubility of levothyroxine sodium .....	13
4.2.3	Determination of permeability .....	14
4.2.4	Overall BCS categorisation and intrinsic dissolution .....	14
4.2.5	Biopharmaceutical Implications: assessment of bioequivalence .....	16
4.3	Stability .....	16
4.3.1	Physical Form and Stability of Levothyroxine Sodium.....	16
4.4	Stability Implications for Formulation, Processing and Packaging .....	17
4.4.1	Solid phase transformation.....	17
4.4.2	Environmental Oxygen and Oxidant Contaminants .....	17
4.4.3	Regulatory Considerations .....	18
4.5	Implications for Product Control Strategy .....	18
4.5.1	Drug Substance – Physical Characteristics .....	18
4.5.2	Drug Product - Assay Limits across Shelf-life .....	18
4.5.3	Drug Product - Dissolution.....	18
4.6	Pharmaceutical Summary and Recommendations .....	19
5	Summary: Clinical and Pharmaceutical Considerations .....	19
6	Overall Summary of Recommendations.....	20
7	Glossary of medical, scientific and regulatory terms .....	21
8	References.....	22

## 1 Lay Summary

Over the past five years MHRA has received an increase in the number of reports from healthcare professionals and patients raising concerns about potential inconsistencies in the quality and effectiveness of different makes of levothyroxine products and even between different batches of the same product. Starting in January 2011, the MHRA has reviewed the medical and scientific literature to assess whether there could be differences in the bioavailability (extent / rate of absorption) of levothyroxine between different tablet products and/or batches, what clinical implications this may have and whether additional controls were needed. This report is a summary of this review which was endorsed by the Commission on Human Medicines, an independent panel of experts who advise the licensing authority.

In the autumn of 2011, there was an unexpected increase in reports from healthcare professionals and patients regarding the Teva Levothyroxine 100mcg Tablet product (marketing authorisation number PL 00289/0039). This led to a separate review of the product, which in February 2012, resulted in the Commission on Human Medicines recommending suspension of the marketing authorisation (meaning that no more of this product could be marketed). Information relating to this suspension will be made available in a separate website publication and for this reason, is not discussed here.

Levothyroxine is not a drug as such but is a naturally occurring thyroid hormone. Therefore, as levothyroxine exists naturally in the body, it can be difficult to establish whether levothyroxine products made by different manufacturers have the same clinical effect (therapeutic equivalence). Guidelines have been issued by the medicines agency of the USA (FDA) which requires a clinical trial comparing blood levels for two or more products (a bioequivalence study). While this approach has some limitations it is considered useful and will be a requirement for any future applications for new levothyroxine medicines in the UK.

There is evidence that some groups of patients (for example those with thyroid cancer, those with heart disease and those who are pregnant) may be particularly sensitive to changes in thyroid hormone and may require close monitoring by their doctors. While most patients seem to tolerate slight changes in levothyroxine dose, or slight changes in their circulating hormone levels without any ill effects, there is literature evidence that in some patients, this may alter their sense of well-being and possibly require their dose of levothyroxine to be altered. As a result, it is important that the quality control tests and limits for each batch of levothyroxine product are stringent and meaningful.

Control tests and limits for levothyroxine are defined by the relevant BP monograph. Current assay limits for levothyroxine sodium tablets are 90.0-105.0% of the declared amount. This gives some allowance for the known instability of the formulated drug substance and is considered clinically acceptable (i.e. variation within these limits is unlikely to have significant clinical effects). Recent pharmaceutical literature shows that levothyroxine sodium has atypical solution properties which suggest that the amount absorbed may be influenced by its dissolution rate (rate at which the drug is dissolved from the tablet dosage form in the gastrointestinal tract). Therefore a discriminatory dissolution test is proposed for inclusion into the BP Monograph.

As formulation ingredients and manufacturing processes may potentially influence bioavailability, any proposed changes to formulation or manufacture will require substantial information to show its acceptability. Any new applications for levothyroxine products will be required to demonstrate bioavailability against a UK branded product.

The Commission on Human Medicines concluded that levothyroxine medicines need not be prescribed by their brand or suppliers name, although this will be kept under review. The full

list of recommendations made by the Commission on Human Medicines is given in section 6 of this report. All of the recommendations have been accepted by the MHRA and the British Pharmacopoeia Commission and are currently being implemented.

## 2 Introduction

### 2.1 Issue

Levothyroxine is an essential medicine for the treatment of underactive thyroid conditions and is very widely prescribed. In 2010, the MHRA estimates that approximately 1,300,000 people took levothyroxine in the UK (source: IMS MIDAS).

This report reviews the physicochemical properties of levothyroxine and what, if any, clinical implications they may have. It is based on a review of published pharmaceutical and clinical literature and summarises an MHRA review that commenced in January 2011 and was endorsed by the Commission on Human Medicines in March 2012.

Levothyroxine tablet products with an approved UK marketing authorisation (product licence) at the time of the review are listed in the table below. Note that not all products with an approved marketing authorisation are marketed.

Table 1 Levothyroxine Tablet Products with an approved UK marketing authorisation (January 2011)

Marketing Authorisation Number	Product Name	Marketing Authorisation Holder
PL 12762/0016	Eltroxin 25 mcg Tablets, Levothyroxine 25 mcg Tablets	Goldshield Pharmaceuticals Limited (now trading as Mercury Pharmaceuticals Ltd)
PL 10972/0031	Eltroxin 50 mcg Tablets Levothyroxine 50 mcg Tablets	Goldshield Group Limited (now trading as Mercury Pharmaceuticals Ltd)
PL 10972/0032	Eltroxin 100 mcg Tablets Levothyroxine 100 mcg Tablets	Goldshield Group Limited (now trading as Mercury Pharmaceuticals Ltd)
PL 00289/0038	Levothyroxine 50 mcg Tablets	Teva UK Limited
PL 00289/0039	Levothyroxine 100 mcg Tablets	Teva UK Limited
PL 00142/0104	Levothyroxine 50 mcg Tablets	Actavis UK Limited
PL 00142/0105	Levothyroxine 100 mcg Tablets	Actavis UK Limited
PL 16201/0001	Levothyroxine 50 mcg Tablets	Forley Generics Limited (now trading as Mercury Pharmaceuticals Ltd)
PL 16201/0002	Levothyroxine 100 mcg Tablets	Forley Generics Limited (now trading as Mercury Pharmaceuticals Ltd)

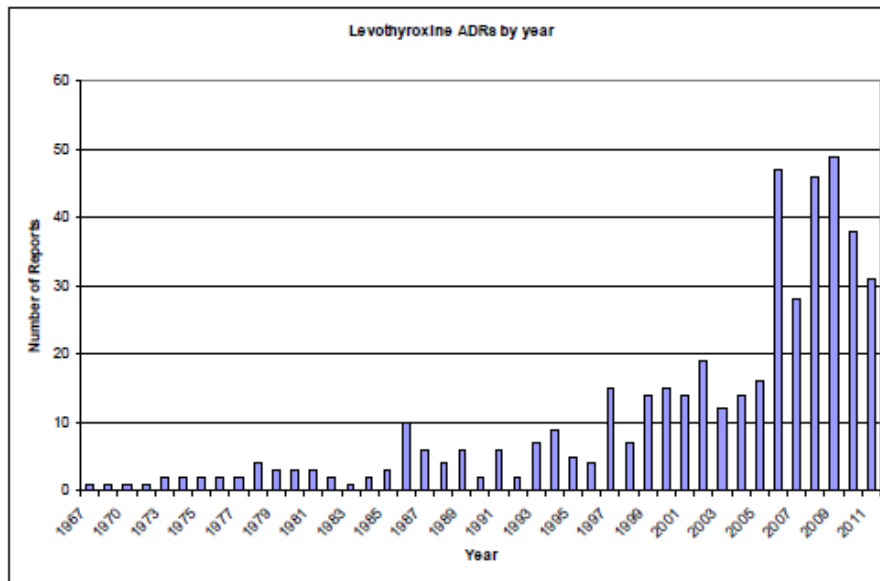
		Pharmaceuticals Ltd)
PL 32446/0001	Levothyroxine Tablets BP 25 mcg	Recipharm Limited
PL 32446/0002	Levothyroxine Tablets BP 50 mcg	Recipharm Limited
PL 32446/0003	Levothyroxine Tablets BP 100 mcg	Recipharm Limited
PL 29831/0130	Levothyroxine 25 mcg Tablets	Wockhardt UK Limited

The MHRA review of marketed levothyroxine tablet products was undertaken following the receipt of a small but persistent number of clinical and quality concerns from healthcare professionals and patients. These concerns focused on whether all tablet formulations of levothyroxine were equivalent and whether possible lack of equivalence might be explained by differences in levothyroxine content. While the number of these reports remains extremely low in comparison to the extent of usage of levothyroxine, queries directed to the MHRA have increased since 2006, suggesting a persistent level of concern from healthcare professionals and the patient population.

For levothyroxine products, these queries are mirrored by Adverse Drug Reaction (ADR or “Yellow Card”) reports which have also increased in the past 4 years as shown in Figure 1. The “Yellow Card” scheme is the UK’s system for collecting and monitoring suspected adverse drug reactions including loss of efficacy and concerns with the quality of medicines. Details on how to submit a “Yellow Card” report are provided in the following link to the relevant area of the MHRA website.

<http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Reportingsuspectedadversedrugsreactions/index.htm>

The reported ADRs cover a wide range, from lack of efficacy and changes in thyroid function tests to nonspecific complaints such as fatigue, alopecia and pain. Out of 453 UK spontaneous ‘suspected’ ADR reports associated with levothyroxine, 87 reports describe reactions of lack of efficacy, product substitution issues, thyroid disorders, and thyroid and pituitary analyses investigation results associated with levothyroxine. In 15 ADR reports the reporter stated that the reactions occurred upon switching between different brands of levothyroxine, and 2 reports relate to issues with interchangeability between liquid and tablet forms. As product names are often not reported, ADRs associated with product interchangeability and/or reformulation may not always be identified.

**Figure 1** Number of ADR received for Levothyroxine Sodium per year

## 2.2 Previous regulatory reviews

In 2009, the MHRA partnered the regulatory authorities of New Zealand (Medsafe) to perform a major review<sup>1</sup> of clinical and quality concerns raised by the marketing authorisation holder and Medsafe regarding an increase in ADR reports following launch of a reformulated levothyroxine product (Eltroxin). Despite thorough review, no root cause could be identified. In general, the scientific and regulatory approach was deemed appropriate, although the use of a European reference product in the bioequivalence study instead of the original New Zealand levothyroxine product was questioned. In the same year, an independent review<sup>2</sup> was performed by the Danish Medicines Agency, also initiated by an increase in adverse events associated with the reformulation of Eltroxin, the brand leader of levothyroxine. In the UK, no changes have been made to either the formulation or method of manufacture of Eltroxin.

For Levothyroxine Tablets BP, the potential impact of the assay (potency) limits in place at that time ( 90.0-110.0% over shelf-life) was reviewed in 2007 by the Medicines for Women's Health Expert Advisory Group, an independent panel of experts that advise the Commission on Human Medicines. The experts were of the opinion that these limits did not pose any clinical risk to the majority of patients. Nevertheless, following consultation with manufacturers, the BP Commission tightened the control limits for assay within the BP Monograph for Levothyroxine Tablets to 90.0 to 105.0 % over shelf-life. These more stringent controls were intended to balance the need to allow for some degradation of levothyroxine during the tablet shelf-life with tighter assay limits to reduce potential variability between products / batches.

## 3 Clinical Review

### 3.1 Overview

A review of published literature was performed to identify the potential clinical consequences arising from variability in potency of levothyroxine products over their shelf-lives, and issues around the bioequivalence and interchangeability of levothyroxine products.

### 3.2 Introduction

The use of thyroid extracts (containing the hormones levothyroxine and liothyronine) as a treatment for hypothyroidism, dates back to 1891. A more pure, synthetic form of levothyroxine was introduced in the 1950s. Despite experiments with liothyronine (T3), alone or in combination with levothyroxine (T4), the latter remains the dominant choice of clinicians and is the current standard thyroid hormone replacement in the UK for the treatment of hypothyroidism.

Once diagnosed, patients normally start the estimated full or just below the full replacement dose immediately unless they are over 50, have severe hypothyroidism or have cardiac problems, in which case, the levothyroxine dose is gradually increased from an initial daily dose of 25 - 50 mcg levothyroxine. This is then increased by 25 – 50 mcg/day at 3-4 weekly intervals until a normal metabolic state is attained.

Thyroid stimulating hormone (TSH) secreted by the anterior pituitary gland, plays a pivotal role in the control of the thyroid axis and serves as the most useful marker of thyroid status. Careful monitoring of serum levels of TSH is necessary until an appropriate dose of levothyroxine is reached. The treatment target is a TSH level within the normal range (0.4 - 4.5 mU/L). TSH is monitored during chronic treatment, usually on an annual basis as chronic under-treatment or over-treatment may be associated with adverse symptoms and undesirable clinical outcomes.

The need for particularly careful dosage titration predominantly applies to thyroid cancer patients who have evidence of residual cancer, elderly patients with underlying cardiovascular disease, pregnant women (where optimal replacement is particularly important in the first trimester to support foetal development) and certain hypothyroid patients who are sensitive to minor fluctuations (either increases or decreases) in their thyroxine levels. For these groups of patients, the content of levothyroxine in the tablet (assay or potency) and bioequivalence (or interchangeability) is extremely important.

If a drug product of significantly 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 significantly greater potency or bioavailability could result in toxic manifestation of hyperthyroidism such as cardiac pain, palpitation, or cardiac arrhythmia.

### 3.3 Is levothyroxine a Narrow Therapeutic Index drug?

Levothyroxine has been referred to as a drug with a narrow therapeutic index (NTI) in several published articles<sup>3 4 5</sup> although this is debatable.



The therapeutic index (also known as therapeutic ratio), is a comparison of the amount of a therapeutic agent that causes the therapeutic effect with the amount that causes adverse reactions. Drugs with narrow therapeutic index are drugs with small differences between therapeutic and toxic doses. There is no agreed European definition but the U.S. Food and Drug Administration (FDA) provides the following definition for a NTI drug:

- a. There is less than a 2-fold difference between the minimum toxic and minimum effective concentrations in the blood,
- and
- b. Safe and effective use of the drug products requires careful titration and patient monitoring.

Acute toxicity and a possible need for therapeutic dose monitoring are usually key characteristics of NTI drugs in practice. However a weekly dose of thyroxine (usually a multiple of the patient's daily dose) has been administered in clinical practice under direct observation, when there are concerns over possible compliance issues; this dosage regimen appears to be well tolerated.<sup>6</sup>

The FDA guidance on bioequivalence studies in levothyroxine advises that a single dose of 600 mcg is administered to healthy volunteers and this dose also appears to be generally well tolerated.

Therefore, acute toxicity with well over double the daily requirement of levothyroxine does not seem to pose safety risks, at least over the short term. In this sense, levothyroxine does not fall into the NTI category.

It has been shown that small changes in serum levothyroxine and liothyronine concentrations, within the normal range, alter serum TSH, indicating a sensitive negative feedback relationship between serum free levothyroxine and TSH.<sup>7</sup> It is possible that in some patients once the optimal dose of levothyroxine has been achieved, they could suffer loss of control of their thyroid disease as a result of any subsequent variability in the amount of levothyroxine administered.

Therefore although levothyroxine does not meet the criteria for being a narrow therapeutic index drug, there are strong indications that small changes in the delivered dose of levothyroxine, should they persist over long term treatment, could have significant clinical consequences.

### **3.4 Stability of levothyroxine over its shelf-life and its clinical consequences**

In response to concerns expressed about levothyroxine sodium products by health care professionals and patients that the potency of levothyroxine tablets may deteriorate prior to its expiry date, the FDA tightened the potency specifications for levothyroxine sodium from 90-110% to 95-105% in October 2007. It was hoped by this means to reduce the variability in the stability profiles between products that could have clinical consequences in achieving target thyroid hormone levels.

In a similar move, the British Pharmacopoeia tightened the upper potency limit over shelf life from 110% to 105%, although the lower limit still remains at 90%.

Under-delivery of levothyroxine as a result of loss of potency over the shelf-life period, while remaining within the BP limits, is not considered to have clinical consequences for the vast majority of patients.

### 3.5 Issues around bioequivalence of levothyroxine products

Currently licensed levothyroxine products in the UK were approved many years ago, under previous legislative requirements. Consequently, these products, which are used interchangeably, are not supported by clinical data such as bioequivalence as expected by today's standards. More recently, applications for marketing authorisations of new levothyroxine products have been supported by bioequivalence data comparing blood levels of levothyroxine for the intended new product with the brand leader. Lack of comparative bioavailability data aside, there are recognised issues with bioequivalence studies involving levothyroxine.

Levothyroxine is not a drug as such but rather a natural hormone. Endogenous thyroxine is indistinguishable from exogenously administered levothyroxine, both in its biochemical characteristics and physiologic effects. Also, continued thyroïdal secretion in study models using healthy volunteers confounds pharmacokinetic data, such as the area under the concentration vs. time curve (AUC; a measure of how much drug has been absorbed) or the maximum plasma concentration (C<sub>max</sub>, a measure of the highest observed drug level in blood plasma). These are the typical parameters that are compared when establishing bioequivalence (interchangeability) between drug products.

A number of methods have been suggested to overcome the uncertainties of demonstrating bioequivalence among levothyroxine products. The current FDA guideline recommends the accepted 2 treatment-2 period-2 sequence crossover design in healthy volunteers using a single larger dose (600 mcg) than is typically used therapeutically. The C<sub>max</sub> and the AUC are calculated for each product with the usual acceptance criteria of 90% confidence intervals of the ratio of test to reference for AUC and C<sub>max</sub> lying within 80% to 125%. The suprathreshold dose of 600 mcg is meant to overcome the potential problems of background endogenous interference and low levothyroxine levels that would follow from lower doses. Whether or not correction for baseline levels should be employed in these studies is still being debated.

Background interference from endogenous levothyroxine could be overcome by recruitment of populations deficient in the endogenous substance under test, however this is not always feasible for practical and/or ethical reasons. Furthermore, heterogeneity in the extent of deficiency among patients may make such a population less well defined and the study less well controlled than when using healthy volunteers. Recruitment of patients on existing replacement therapy may be complicated by variable baseline control.<sup>8</sup>

Thyroid stimulating hormone (TSH) has been proposed as an alternative biochemical marker for levothyroxine in bioequivalence studies, based on the fact that attaining TSH levels in the normal reference range is the biochemical target of levothyroxine treatment and is used to guide levothyroxine replacement dosage. However, as Mayor<sup>8</sup> and other authors<sup>9</sup> have demonstrated, the variability associated with TSH, as a secondary effect, is extremely high (CV of up to ~200% reported in these studies), while variability was also noted for total triiodothyronine.

Considering the above limitations in establishing bioequivalence for levothyroxine products, the clinical implications of switching from one make of levothyroxine to another remain unclear.

In the USA, the American Association of Clinical Endocrinologists, American Thyroid Association (ATA), and The Endocrine Society have collaborated to create a survey that sampled 18,000 reports of the clinical experience of their society members and frequent prescribers of levothyroxine<sup>10</sup>. The survey provided an opportunity to collect clinical observations of adverse events or product availability problems from physicians caring for patients with thyroid disease who required use of levothyroxine preparations.

From this survey, a total of 1536 responses were received; most responses (971 of 1,536; 63.2%) reported no adverse events had been observed. After adjustment for known reasons for unstable thyroid function tests results, 199 reports of adverse reactions associated with changes in TSH values were further analysed. Of these, 177 reports (88.9%) were associated with a change to a different make of levothyroxine tablet; in 21 cases (10.6%) no change was noted when the subject used a different make of tablet. These data suggest that adverse events in this survey were far more commonly seen when switching between products compared to repeat use of the same product.

The commentaries accompanying these reports identified several potentially serious consequences of suboptimal levothyroxine therapy in vulnerable populations, including recurrence of cancer associated with unexpected TSH elevation, atrial fibrillation in older patients who were exposed to excess thyroxine, and potential life-long consequences in very young patients with loss of therapeutic control of congenital hypothyroidism. Because the authors specifically eliminated pregnant patients from final reporting, the results are limited regarding this vulnerable group. Data from a similar systematic survey in the UK is currently lacking.

For historical reasons and in common with many older products, clinical demonstration of bioequivalence of UK levothyroxine products is not available. For immediate release tablet products, such as levothyroxine, safeguards for equivalence are reliant upon suitable quality specifications (the tests and limits applied at batch release over shelf-life). As a minimum, this must comply with the BP monograph for Levothyroxine Tablets. However during the MHRA's review it was established that additional measures were required due to the atypical nature of the active substance. This is discussed in section 4.

### **3.6 Discussion and Conclusions**

Although levothyroxine does not fulfil the criteria for being a narrow therapeutic index drug, there is evidence that in at least some patients, precise dosing over the long-term is critical.

Small changes in serum levothyroxine and triiodothyronine concentrations alter serum TSH. Individual response to slight changes in the amount of levothyroxine delivered to the body can be variable and there is literature evidence that in some patients, a small change in the amount of levothyroxine can alter their general sense of well-being and possibly lead to subclinical thyroid disease although this is not universally supported by experts.

Typically in Europe, assay limits for medicines that do not have any stability issues are 95.0 – 105.0% of label claim over shelf-life. However, wider limits may be justified, particularly where the drug product is known to lose some potency on storage. This situation is unavoidable for many medicines where the drug substance is easily degraded and this is certainly the case for levothyroxine.

In line with the BP Monograph, the upper potency limit of UK levothyroxine tablets over their shelf-life is 105.0 % of label claim. Tightening the lower potency limit of 90.0% was not considered clinically meaningful by the Commission on Human Medicines; therefore limits of 90.0 – 105.0% have been retained. These limits also ensure that a sufficient shelf-life is maintained to allow time for manufacture, distribution and storage within warehousing / pharmacies. This helps to ensure that the product remains available to patients and is capable of being manufactured to achievable quality standards.

To assure that different levothyroxine products are interchangeable, it is considered more important that their dissolution characteristics are satisfactorily equivalent, using a suitable and discriminative test method. This recommendation has been acted upon by the British Pharmacopoeia Commission and is discussed further in section 4.

Establishing bioequivalence and its correlation to *therapeutic equivalence* for endogenous substances in general, and for levothyroxine in particular, continues to be a challenge. Demonstrating bioequivalence according to the guidelines issued by the FDA should provide some reassurance that a new levothyroxine product is bioequivalent to a currently licensed levothyroxine product. Bioequivalence data between currently licensed levothyroxine products are not available; however it is considered that more stringent quality standards, particularly the introduction of a discriminatory dissolution test will improve assurance of interchangeability between products.

## 4 Pharmaceutical Quality Aspects

### 4.1 Overview

Levothyroxine sodium has been formulated into tablets to treat thyroid disease for over 50 years. A review of the scientific literature highlights the known chemical instability of levothyroxine once it is formulated as a product (e.g. an oral tablet or oral liquid). There are also reports of formulation-related variability, where differences between the non-active ingredients (excipients) in different tablet products can cause changes in therapeutic response.

The MHRA reviewed scientific publications in order to evaluate whether the reported challenges surrounding levothyroxine products (e.g. potency, interchangeability as highlighted in section 2) may be linked to the physicochemical and biopharmaceutical properties of the drug substance. Key considerations for formulation, processing, packaging and control strategy of levothyroxine products are discussed, together with implications for regulatory management.

### 4.2 Bioavailability and Bioequivalence: Solubility, Permeability and Dissolution Rate

#### 4.2.1 Background

In order for a drug substance in solid form to be absorbed from the gastro-intestinal tract, it must first pass into solution. This process, known as “dissolution”, may be influenced not only by the fundamental physico-chemical properties of the drug substance, but also by physical factors such as its particle size distribution and surface area and by other constituents of the dosage form in which it is incorporated (its formulation as a tablet for example). Thus bioavailability may be dependent on the extent to which these factors affect the rate of dissolution of the drug substance. Generally, drug substances that have high aqueous solubility are not associated with dissolution-rate limited bioavailability or with formulation-associated variability in clinical response. However drug substances that have a low aqueous solubility may be sensitive to variability in clinical response, linked to the dissolution of the drug substance from the dosage form.

Intestinal permeability is a measure of the rate of transfer of a drug substance in solution across human intestinal membranes. Permeability and solubility together form the basis of the Biopharmaceutics Classification System (BCS)<sup>11</sup> which is a widely used methodology for classification of orally administered drug substances. The principles of BCS may be utilised to determine when a waiver for *in vivo* bioequivalence studies may be justified, together with the likelihood that formulation may impact relative bioavailability.

According to the BCS, drug substances may be classified as follows:

- Class I - High Permeability, High Solubility
- Class II - High Permeability, Low Solubility
- Class III - Low Permeability, High Solubility
- Class IV - Low Permeability, Low Solubility

For the purposes of BCS classification and in line with the EU “Guideline for Investigation of Bioequivalence”<sup>12</sup>

- A drug substance is considered “highly soluble” when the highest dose strength is soluble in 250 ml of buffer over a pH range of 1 to 6.8 (at least pH 1, 4.5 and 6.8) at  $37 \pm 1^\circ\text{C}$ .
- A drug substance may be considered highly permeable when the measured extent of absorption in humans is determined to be  $> 85\%$  of an administered dose, based on mass-balance or in comparison to an intravenous reference dose.
- A drug product is considered to be “very rapidly dissolving” when  $> 85\%$  of the labelled amount of drug substance dissolves within 15 minutes using Ph. Eur. paddle apparatus (50 rpm) or basket apparatus (100 rpm) in a volume of  $< 900$  ml buffer media of pH 1, 4.5 and 6.8 without surfactant. This is accepted as approximating to T50% gastric emptying time (the time taken to empty 50% of a 200 ml volume of water from the stomach under fasting conditions).

#### 4.2.2 Determination of solubility of levothyroxine sodium

The published scientific literature varies widely in the descriptions of solubility of levothyroxine sodium. One report<sup>13</sup> estimates the aqueous solubility of levothyroxine at 0.15 mg/ml (150 mcg/ml). Based on relatively high estimates of aqueous solubility and permeability (calculated log P of 3.51), the same reference categorises levothyroxine sodium as belonging to the highly soluble and highly permeable category of the Biopharmaceutical Classification System (BCS Class I). For molecules that are classified as highly soluble and highly permeable, formulation and process variables would generally be expected to have a negligible impact on bioavailability. However, based upon reports in the published literature and those made directly to the MHRA, this would not seem to be the case for levothyroxine sodium.

A detailed consideration of the kinetics of levothyroxine degradation has been published<sup>14</sup> that includes assessment of the pH-solubility profile, which decreases over a physiologically relevant pH range of 1 – 6. This same paper<sup>14</sup> reports a much lower intrinsic solubility value of 0.25 mcg/ml (pH range of 3-6).

The pH of human stomach contents is generally around pH 1 to 2 without food and may increase up to pH 5 with food. A potential decrease in dissolution rate with increasing pH is in line with current prescribing advice to take levothyroxine on an empty stomach. This also provides a putative rationale for reports of decreased response in patients with conditions / concomitant treatments that raise gastric pH.<sup>15</sup>

Structurally, levothyroxine is described<sup>14</sup> as amphiphilic in nature, containing a hydrophobic benzyl moiety coupled to three ionisable, hydrophilic amine, carboxylate and phenolic moieties. A study<sup>16</sup> has confirmed aggregation (50-100 nm in radii) of levothyroxine sodium in aqueous solutions, enabling apparent solubility of  $> 1.5$  mg/ml to be achieved.

The formation of such soluble aggregates is a possible explanation of the discrepancy between published determinations of aqueous solubility. The true solubility of levothyroxine (the maximum dissolved concentration of the monomer) is likely to be less than 1.5 mg/ml. While deaggregation kinetics are not discussed within this paper, the solubility of the monomer is expected to determine the concentration of levothyroxine sodium that is available for absorption.

The same study<sup>16</sup> describes the intrinsic dissolution rate (dissolution of the drug substance itself without any other ingredients) of levothyroxine sodium as surprisingly slow at  $\sim 0.0002$  mg/min/cm<sup>2</sup> over a physiologically relevant pH range. Typically, intrinsic dissolution rates should be greater than 0.1mg/min/cm<sup>2</sup> for a compound to be considered rapidly dissolving<sup>17</sup>.

These data suggest levothyroxine cannot be classified in this way and should not be regarded as meeting the solubility criteria for classification under BCS Class I or III. This is supported by published data<sup>18</sup> for an immediate release tablet formulation, where dissolution performance is shown to be extremely low in dissolution media without surfactant.

#### 4.2.3 Determination of permeability

Despite a calculated log P for levothyroxine of >3.0, there are reports of limited permeability, which may contribute to variable absorption. Recent authors have linked potential poor intestinal permeability with variable bioavailability and assessed co-administration with fatty acids as a means to improve intestinal epithelial transport.<sup>19</sup>

A soft gelatin capsule formulation of levothyroxine, containing levothyroxine dissolved in glycerin (Tirosint®) has been shown<sup>20</sup> to give a more consistent *in vitro* dissolution pattern however the impact upon bioavailability *in vivo* remains a matter of speculation.

#### 4.2.4 Overall BCS categorisation and intrinsic dissolution

The potential advantages of basing BCS categorisation on intrinsic dissolution rate rather than on equilibrium solubility determinations has been discussed in a paper<sup>21</sup> by Yu *et al.* For levothyroxine where the maximum daily dose is relatively low, this may avoid inadvertent classification as “highly soluble” where intrinsic dissolution rates strongly suggest that a more cautious approach is warranted. Particularly for amphiphilic molecules, where a tendency to self-aggregation complicates conventional determinations of solubility, this approach may be more logical.

Based upon the reported slow intrinsic dissolution rate and product dissolution performance that would not meet the standard pharmacopoeial criteria for rapidly or very rapidly dissolving, it is likely that *in vivo* absorption may be dissolution rate limited. For products with known dissolution rate-limited bioavailability, the formulation ingredients and/or manufacturing process may impact the rate and extent of absorption. In the case of slow dissolving molecules such as levothyroxine, use of micronised drug substance and the presence of water-soluble, rapidly dissolving excipients in the formulation would be expected to have a beneficial impact on formulation dissolution rate and thus bioavailability.

The Laboratories of the MHRA (Medicines Testing Scheme, Teddington) obtained samples of representative levothyroxine solid oral dosage forms from UK Pharmacy dispensing stock. The MHRA Laboratory then performed dissolution studies in 0.1M hydrochloric acid and in water (Ph. Eur. Dissolution Apparatus 2; 50 rpm)

According to the Guideline for Investigation of Bioequivalence, a rapidly dissolving drug product is one that shows 85% dissolution in 15 min under these test conditions. Such a drug product is generally believed to behave as a solution, thus bioavailability of the drug is highly unlikely to be dissolution rate limited.

Results demonstrated that none of the products marketed in the UK met these criteria, thus supporting the contention that dissolution performance may be rate-limiting for absorption.

The MHRA Laboratories then examined a range of dissolution conditions before identifying a method that balanced a reasonable extent of release with maximum discrimination (the ability to distinguish between formulations). **It is very important to note that apparent differences in dissolution performance do not necessarily equate to differences in bioavailability or therapeutic effect.**

The dissolution of representative samples of UK levothyroxine products under these conditions are given in tables 2 - 3. Standard error bars are included where multiple batches were tested.

Table 2

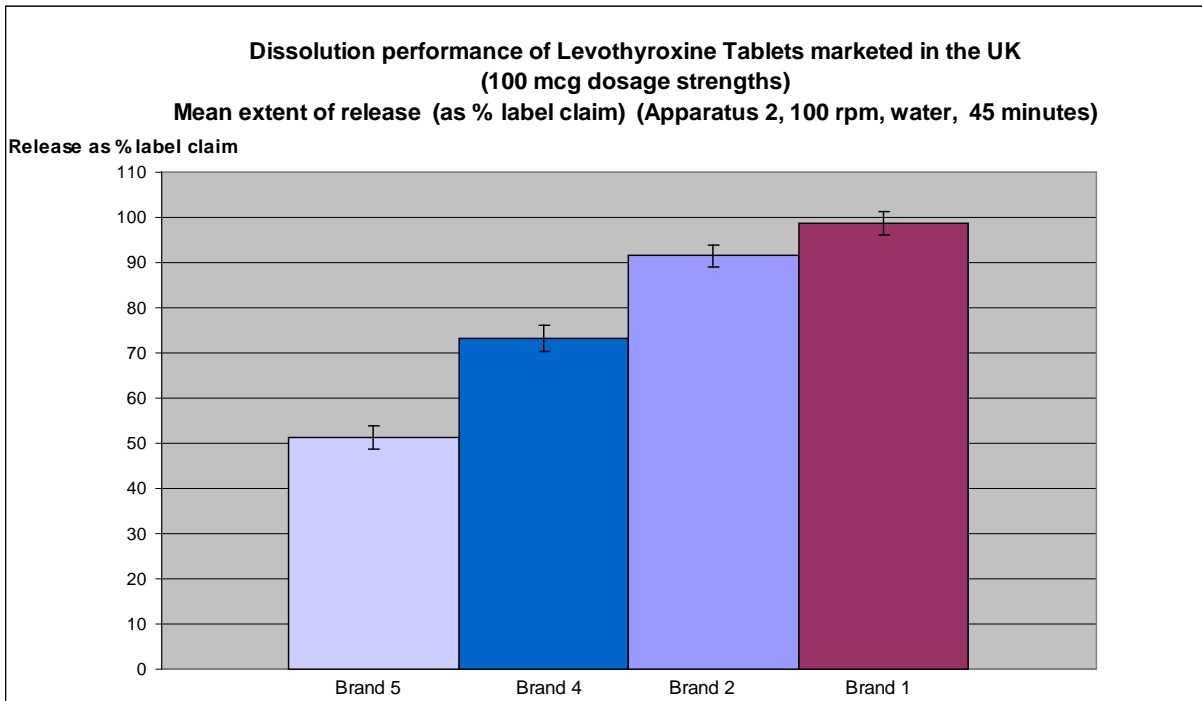
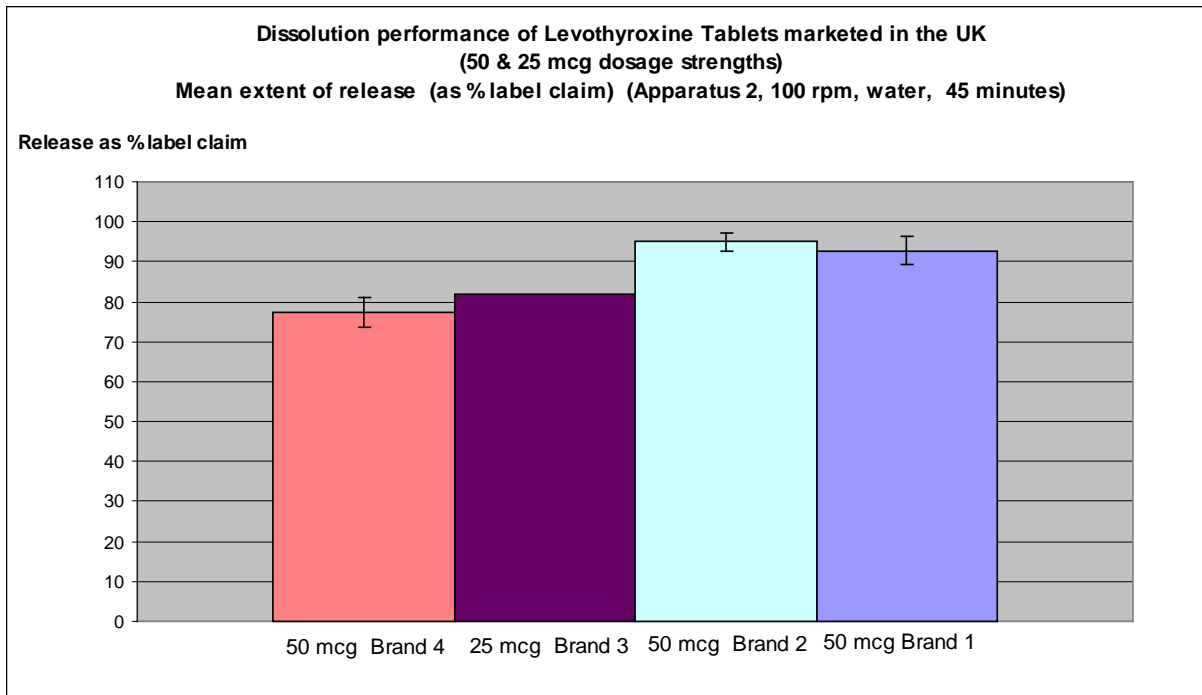


Table 3





These findings have formed the basis of a proposed dissolution method and specification for inclusion in the BP Monograph for Levothyroxine Tablets.

#### 4.2.5 Biopharmaceutical Implications: assessment of bioequivalence

It is apparent from scientific literature that levothyroxine sodium has atypical solution properties coupled with an extremely slow intrinsic dissolution rate. As a result, a BCS-based biowaiver for bioequivalence to reference products will not be accepted for any new application for a marketing authorisation.

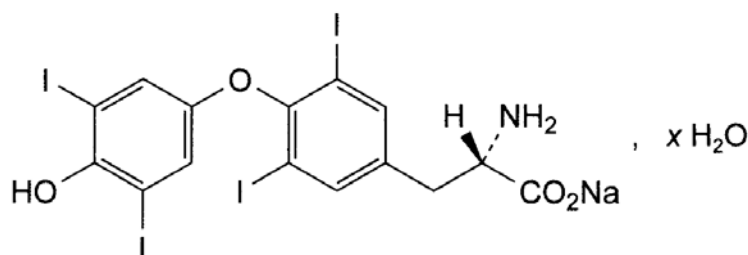
### 4.3 Stability

For solid oral dosage forms, a growing body of evidence links the physical form and hydration state of the drug substance to its subsequent stability. Particularly once formulated, levothyroxine has a complex stability profile and has been reported to be sensitive to some common excipients, light, temperature, moisture, pH and environmental oxygen.

#### 4.3.1 Physical Form and Stability of Levothyroxine Sodium

The chemical structure of levothyroxine sodium is shown below. The European and British Pharmacopoeias specify “a variable amount of water” ranging between 6.0 - 12.0%, in line with this drug substance existing primarily in its pentahydrate form.

Figure 2 Chemical structure of levothyroxine sodium



Levothyroxine sodium pentahydrate is reported as stable for > 4 years when stored at 25°C/60%RH<sup>16</sup> and for 6 months at 40°C/75%RH<sup>22</sup>. However, stability studies performed at 50-80°C for 7 days<sup>14</sup> in the presence of air, show that at temperatures exceeding 60°C, sodium levothyroxine rapidly degrades, exhibiting biphasic degradation kinetics.

Its physical stability has been characterized as a function of temperature by thermal analytical methods such as differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA)<sup>16,22,23</sup> In an atmosphere of dry nitrogen; the pentahydrate undergoes a three-step dehydration to form a dihemihydrate, a monohydrate and finally an amorphous form. Thermal analytical data suggest that levothyroxine is physically stable in its pentahydrate form below 50°C, but at higher temperatures, when exposed to air, undergoes rapid dehydration, followed by degradation.

Oxidative degradation of the dehydrated form may explain the discrepancy between the work of Collier *et al*<sup>23</sup>, which suggested that levothyroxine sodium was stable in its dehydrated form, on the basis of storage and subsequent analysis under dry nitrogen and those of Levans *et al*<sup>6</sup>, where dehydrated and amorphous forms exposed to atmospheric air were reported to undergo rapid oxidative degradation, making them difficult to isolate.

In the case of hydrates such as levothyroxine sodium, understanding the physical stability of the drug substance may be pivotal to ensuring adequate chemical stability of the formulated product during manufacture and throughout shelf-life. Conditions to maintain physical stability should be carefully defined prior to process design.

#### **4.4 Stability Implications for Formulation, Processing and Packaging**

Since the physical state of any drug molecule in a medicinal product may influence its manufacturability, stability and bioavailability, it is imperative that formulations of levothyroxine contain primarily the pentahydrate crystal form and are manufactured and stored under conditions that maintain its physical stability to the greatest extent possible.

##### *4.4.1 Solid phase transformation*

Most pharmaceutical manufacturing processes carry some risk of inducing solid-phase transformation into a less stable form and this is particularly the case for hydrates such as levothyroxine sodium. From the perspective of regulatory assessment; should milling of the drug substance or the manufacturing process of the drug product inadvertently generate the lower hydrates or amorphous forms of levothyroxine sodium, the resulting formulation may have a greater tendency to degrade rather than recrystallise to the stable pentahydrate, crystalline form. Therefore, for molecules such as levothyroxine, careful risk-analysis of each pharmaceutical unit manufacturing operation is necessary to ensure consistent and optimal stability performance of the product.

In light of its high potency, low content and instability, there are significant manufacturing challenges associated with levothyroxine products. Solid dose formulations of levothyroxine frequently utilise wet granulation processes to achieve an acceptable content uniformity. Ideally, processes which expose the active substance to moisture / energy followed by concomitant drying will be extensively characterized and optimised with respect to stability performance in addition to content uniformity; the resulting critical process parameters should form part of any regulatory package either for initial registration or for any subsequent variations to the manufacturing process. Particularly for granulation and drying processes, comprehensive process and equipment validation are essential to ensure reproducible manufacture. Attention must be paid to temperature and humidity controls during storage of bulk tablets, shipment and warehousing.

Exposure to high humidity is recognized as a risk factor for most unstable formulations and thus is generally adequately controlled. However, potential loss of water of hydration, resulting from aggressive drying processes, particularly at temperatures > 50°C may have a critical impact on stability and may explain inconsistent or batch variability in stability profiles. Exposure to low humidity such as may result from addition of desiccant sachets to primary packaging may also lead to dehydration and degradation.

##### *4.4.2 Environmental Oxygen and Oxidant Contaminants*

Particularly in the solid state, the potential sensitivity of levothyroxine to temperature and environmental moisture has been widely discussed; however a mechanistic sensitivity to

oxygen predicted by solid phase degradation pathways and confirmed by thermal analytical studies with and without oxygen may be insufficiently recognised. While requiring evaluation on a case-by-case basis, the use of oxygen scavenging packaging may also be valuable in this regard.

Excipients which may carry significant amounts of oxidising impurities may contribute to batch to batch variability in levothyroxine stability profiles, as a result of direct oxidation.

#### 4.4.3 Regulatory Considerations

Given the potential sensitivity of levothyroxine products to apparently minor changes in processing technology, the manufacture of levothyroxine products should be considered “non-standard” despite using conventional blending, granulation and compression technology.

### 4.5 Implications for Product Control Strategy

#### 4.5.1 Drug Substance – Physical Characteristics

In light of the low intrinsic dissolution rate, the specification for the drug substance should include suitable control limits for particle size distribution. A number of micronised grades of levothyroxine sodium pentahydrate are available; multi-point control limits sufficient to describe the particle size distribution should be proposed and justified, ideally with reference to lots for which bioequivalence or bioavailability has been demonstrated.

#### 4.5.2 Drug Product - Assay Limits across Shelf-life

As discussed earlier in this report, while levothyroxine is not considered to have a narrow therapeutic index, precise dosing is crucial to maintain a patient's quality of life and to avoid long-term side effects. This was recognised in 2007, when an Expert Advisory Group to the BP Commission considered input from manufacturers and the action by the USP to tighten assay limits across shelf-life. They recommended that “to address any potential clinical concerns whilst avoiding placing a prohibitively restrictive burden on manufacturers, limits of 90.0 to 105.0 % should be adopted”. This recognised that levothyroxine sodium degraded on storage, but also recognised the concerns over the therapeutic range of the product and reflected the data provided by manufacturers. Re-examination of these limits in March 2012 by the Medicines for Women's Health Expert Advisory Group and the Commission for Human Medicines has confirmed that these limits are considered appropriate; variation within these limits are highly unlikely to be clinically significant.

#### 4.5.3 Drug Product - Dissolution

An understanding of the dissolution performance of formulated levothyroxine sodium is essential, particularly in light of the low intrinsic dissolution and the potential impact of formulation on the *in vivo* release profile. The BP Commission has developed draft dissolution limits and conditions for inclusion within the BP Monograph for Levothyroxine Tablets; this is currently published for consultation with the pharmaceutical industry, interested organisations and the general public.

In light of the finding that the inclusion of a surfactant such as sodium dodecyl sulphate dramatically enhances dissolution<sup>18</sup> and in some cases has been demonstrated to negatively impact discrimination<sup>24</sup>, dissolution media containing a surfactant is not permitted for control of levothyroxine products.

#### 4.6 Pharmaceutical Summary and Recommendations

Levothyroxine has atypical solution properties that may result in it being incorrectly regarded as a highly soluble molecule when strong evidence exists to support dissolution-rate limited bioavailability. As with any substance that exhibits dissolution-rate limited bioavailability, formulation ingredients and manufacturing process may impact on *in vivo* performance.

The solid-state chemical stability of levothyroxine is influenced by its physical form. The interdependence of the physical and chemical stability properties makes it imperative that this relationship be factored into the design and interpretation of both drug substance and formulation stability.

- Given the potential sensitivity of levothyroxine products to apparently minor changes in processing technology, the manufacture of levothyroxine products should be considered “non-standard” despite using conventional blending, granulation and compression technology. Therefore minor changes in process technology or scale, even if this is less than a 10-fold change, will require to be supported by appropriate validation and stability data.
- Given the atypical solution properties of levothyroxine sodium, coupled with its extremely slow intrinsic dissolution rate, acceptance of a BCS-based biowaiver for bioequivalence to reference products will not be accepted for any new application for a marketing authorisation.

### 5 Summary: Clinical and Pharmaceutical Considerations

The effects of levothyroxine therapy are monitored by adjusting dosage when necessary to keep the patient’s TSH levels within a “normal” range (0.4 - 4.5 mU/L). This is particularly important for a subset of patients that may be more sensitive to levels of thyroid hormone (those with thyroid cancer, those with heart disease and those who are pregnant).

Levothyroxine Tablets are difficult to manufacture and may be prone to instability once formulated. However, tighter controls on the quality of the tablet in the form of a discriminating dissolution test and limit will be implemented to minimise potential for variability between products and batches. Similarly, additional regulatory expectations are proposed regarding the extent of data generated to support apparently minor and more major changes in manufacture and to support the introduction of new levothyroxine products.

These are reflected in recommendations of the Commission on Human Medicines which are listed in full in the following section.

## 6 Overall Summary of Recommendations

The Commission on Human Medicines has made the following recommendations; all of which have been adopted by the MHRA:

1. With respect to the current pharmacopoeial standards for levothyroxine drug products, the introduction of a suitable discriminatory dissolution test and control limits is recommended.
2. Acknowledging standard prescribing practice and that this drug product has been prescribed on a generic basis for many years, brand or named supplier prescribing is not considered necessary at this stage, but should be kept under review.
3. Submission of a request to the European Pharmacopoeia Commission to specifically reference the pentahydrate form in the Ph. Eur. Monograph for Sodium Levothyroxine is recommended for consideration by the BP Commission.
4. The introduction of a pharmacopoeial standard (Monograph) for levothyroxine oral solution drug products within the British Pharmacopoeia is recommended.
5. Given the potential sensitivity of levothyroxine products to apparently minor changes in processing technology, the manufacture of levothyroxine products should be considered “non-standard” despite using conventional blending, granulation and compression technology. Therefore changes in process technology or scale, even if this is less than a 10-fold change) will require to be supported by appropriate validation and stability data, including dissolution profiling.
6. Minor formulation and manufacturing changes may have a major impact on the quality, safety and efficacy. As such these changes should most appropriately be submitted as Type 1B or Type II variations rather than Type IA as defined by Annex II of the variation regulation (Commission Regulation (EC) 1234/2008).
7. Given the atypical solution properties of levothyroxine sodium, coupled with its extremely slow intrinsic dissolution rate, acceptance of a BCS-based biowaiver for bioequivalence to reference products for an abridged submission or to “bridge” to published data under a legal basis of Article 10a (well-established use) is not appropriate.
8. Major formulation and manufacturing changes should be supported by bioequivalence studies.
9. Levothyroxine should be prescribed and dispensed in quantities covering three months supply, where appropriate, in order to address issues of continuity of supply and also to improve convenience to patients.
10. Whilst recognising the difficulties in establishing bioequivalence for levothyroxine as an endogenous substance, the CHM consider that bioequivalence studies in line with the FDA guidelines are of value providing some reassurance of bioequivalence.
11. A similar review of liothyronine products is recommended

## 7 Glossary of medical, scientific and regulatory terms

This glossary is intended to provide definitions of some of the scientific terms used in this report. These terms are defined **in the context of this report** only.

Term	Definition
Bioavailability	The degree to which or rate at which a drug substance is absorbed or becomes available at the site of physiological action.
Bioequivalence	A pharmacokinetic term used to assess the expected biological and clinical equivalence of two medicinal products. If two products are said to be bioequivalent, they are expected to have the same therapeutic effect.
Dissolution	The rate and extent to which a solid drug substance presented as a drug product passes into solution.
Intrinsic dissolution	The rate and extent to which a pure, solid drug substance passes into solution, when conditions such as surface area, agitation-stirring speed, pH and ionic strength of the dissolution medium are kept constant.
Label claim	The theoretical content of drug substance per unit does e.g. the label claim of a levothyroxine 100 microgram tablet is 100 microgram of levothyroxine sodium.

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