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Escitalopram: An Application for SPC Refused due to Previous Registration of the Racemic Drug

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The Israeli Patent office recently refused H. Lundbeck's application to extend the term of its Israeli patent[1], covering its blockbuster drug *Cipralex*® whose active pharmaceutical ingredient is the single (*S*)-enantiomer[2] (escitalopram) of the racemate Citalopram[3]. The refusal was based on the Israeli Registrar's conclusion that the first registration of a drug containing escitalopram by the Israeli Ministry of Health was the previous registration of the racemate (Citalopram, marketed as *Cipramil*®)[3]. This holding is, with respect, erroneous, for reasons on which we expand below.
An appeal on the Decision is pending before the District Court.

THE ISSUES AND THE HOLDING

(I) BACKGROUND

Lundbeck owned a previous patent[4] covering certain intermediates and a process for manufacturing the racemate citalopram. Lundbeck registered a drug containing the racemate with the Israeli Ministry of Health and marketed same by the commercial name *Cipramil*®[3].

Lundeck later developed a drug containing the *(S)*-enantiomer of citalopram as an API, namely Cipralex®. The issue at hand was Lundbeck's application to extend the term of its patent covering said enantiomer[1].

Oppositions to Lundbeck's PTE application were lodged by Unipharm Ltd. (an Israeli generic company) and by the Chemistry and Pharmaceutics Society of the Manufacturers Association of Israel (which often also sides with the Israeli generic industry).

The opponents raised three arguments:
(a) that the date for filing the PTE application was erroneously extended by the PTO; **(b)** that the patent is ineligible for PTE, because the first registration of escitalopram is *Cipramil*® and not *Cipralex*®; **(c)** that the PTE application was filed in bad faith and through misrepresentations, because Lundbeck failed to disclose its previous registration of *Cipramil*® as a registration of a drug containing the escitalopram.

The Israeli Registrar of Patents rejected the first argument, but accepted the second and allowed the opposition. The third argument was therefore moot and was not decided.

1 IL Patent No. 90465 (claiming priority from a 1984 patent application).
2 Escitalopram oxalate. In certain other countries, such as the U.S. and Australia, it is marketed under the name *Lexapro*®. Other commercial names are used in different countries.
3 Citalopram HBr marketed under the name Celexa (Forest Labs) or Cipramil (Lundbeck)
4 IL Patent No. 75690 (claiming priority from a 1984 patent application).

(II) WHAT IS THE FIRST REGISTRATION OF A "SUBSTANCE"

Among the conditions for a grant of a patent term extension in Israel there are two that relate to the registration of the drug in the Israeli Register of Drugs.

- A drug containing the "Substance" (as such term is defined and will be immediately explained) must be registered in the Register of Medical Preparations under section 47A of the Pharmacists Ordinance [New Version], 1986[5]; and
- said registration must be ***"the first registration that allows the Substance to be used in Israel for medical purposes"***[6].

The term "Substance" is defined[7] as "the active ingredient of a drug or salts, esters, hydrates or crystal forms of that ingredient". Note that the law refers to the "active ingredient" and not to the "active moiety". In addition, the definition of a "Substance" does not refer to enantiomers and racemates, although chirality and stereoselectivity were well known in 1998, when the law was enacted[8].

It follows that, in order for a patent claiming an API or a drug, to be eligible for patent term extension in Israel, the registration of the drug must be the first registration of a drug containing the active pharmaceutical ingredient of that drug.

The opponents argued that the API of *Cipramil*® is in fact escitalopram, because the *(R)*-enantiomer was essentially inactive[9]. According to the opponents, it is the racemate drug *Cipramil*® and not the single enantiomer drug *Cipralex*® that is the first registration of escitalopram and that allowed use of escitalopram for medical purposes in Israel. The parties adduced substantial expert opinions concerning the scientific and regulatory issues involved in the development of *Cipralex*® (including, among others, on the question whether the *(S)*-enantiomer is more efficacious than the racemate whether the *(R)*-enantiomer inhibits the effect of the *(S)*-enantiomer, and whether the clinical development of *Cipralex*® was shortened in view of the previous registration of *Cipramil*®)

The Registrar did not resolve these questions, in formulating his sweeping decision.

The Registrar **held** that a racemate should be viewed as a "combination" of two substances, the *(S)*-enantiomer and the *(R)*-enantiomer. Based on this premise, it was easy for the Registrar to hold that even if the *(S)*-enantiomer has certain advantages over the racemate, that is irrelevant, because the registration of the drug "containing" the racemate was a previous registration of a drug "containing" the *(S)*-enantiomer. It is also not surprising that the Registrar viewed the situation at hand as a "mirror situation"[10] of the question he dealt with in the **Novartis (2005)**[11] case.

In the **Novartis** case, the Registrar held that a new drug containing a combination of two previously registered different APIs does not give ground for extension of the term of a new patent claiming the combination and that the new combination cannot be deemed a new "Substance"[12].

[5] Section 64D(2) of the Patents Law, 1967 **("the Patents Law").**

[6] Section 64D(3) of the Patents Law.

[7] Section 64A of the Patents Law.

[8] Let alone in 2005, when the definitions relating to PTE were amended.

[9] It is interesting to note that in the U.S., Teva (through Ivax) attacked that validity of the corresponding U.S. patent (RE 34,712) on the ground that a prophetic prior art that predicted (incorrectly) that the ***(R)*-enantiomer** of citalopram would be more effective anticipates escitalopram. See **Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc.**, 501 F.3d 1263

[10] Pun is in the original decision.

[11] An application by Novartis AG to extend the term of IL Patent No. 97219 (26 Dec., 2005); Appeal dismissed – M.A. (TA) 1063/06 **Novartis AG v. The Registrar of Patents** (26 Feb., 2007).

[12] For further details regarding the **Novartis** decision, see our newsletter dated January 2006.

The Israeli Registrar was mindful of the fact that his conclusions may be viewed as contradicting the initial premise of validity of the *(S)*-enantiomer patent, namely, that escitalopram is novel over the racemate. In dealing with this issue, the Registrar held that the questions at hand (patentability and eligibility for PTE) are different. According to the Registrar, even if the resolution of an enantiomer from a racemate is inventive, this does not change the fact that the API in the racemate was escitalopram. Likewise, even if one were to accept that escitalopram is more efficacious than the racemate, that may be relevant only for patentability, but not for the purpose of PTE. The Registrar equated this situation with the situation of a previously registered impure drug, and a later development of a pure drug (the *(R)*-enantiomer being deemed as the impurity in the racemate). In such a case, the Registrar explained, a patent may be granted for the new (more) pure API but a PTE application must be refused.

The Israeli Registrar was also mindful of the fact that the Ministry of Health regards escitalopram as a New Chemical Entity (and distinguished from the racemate), but again he did not view this as a reason to change his conclusion.

(III) EXTENSION OF THE DEADLINE FOR FILING THE PTE APPLICATION

Due to a mistake, Lundbeck was late in filing its PTE application. The Registrar allowed Lundbeck's application to extend the time[13] and allow the late application[14]. After examination, the application was published for opposition. During the course of the opposition, the opponents argued that the extension of time order should not have been granted. The Registrar dismissed this argument, having found that his previous decision was justified. This part of the decision is less interesting, except, perhaps, for the fact that the Registrar was willing to listen to this argument.

It is not at all clear that this argument may be raised in an opposition to a PTE application[15]. However, this was the "law of the case", because the Registrar's deputy refused, at the time, to allow Unipharm to join the application to extend the time for filing the application and, in his decision, he noted that Unipharm will be entitled to raise these arguments during to the opposition to the PTE application itself[16].

COMMENTS

It is submitted that, with respect, the Registrar erred in his decision.

The legal conclusion that racemic *Cipramil*®'s registration should be deemed as the first registration of the single enantiomer escitalopram is also, with respect, flawed and tainted with hindsight.

(I) THE "SUBSTANCE" (API) OF A RACEMIC DRUG IS THE RACEMATE AND THE API OF A SINGLE ENANTIOMERIC DRUG IS THE ENANTIOMER

When the notional person skilled in the art examines a patent application disclosing a racemate, he or she regards **the racemate** as the API (and not its putative enantiomers).

[13] Restitutio in integrum.

[14] In a decision dated 15 June, 2005.

[15] It is not listed as a ground for opposition in Section 64G of the Law and it would seem that an interested person should file an application for leave to appeal, 30 days after the date of the order.

[16] In his decision dated 27 March 2005.

Admittedly, the person skilled in the art will know when reviewing a chemical structure of a compound having at least one stereogenic center the possible stereoisomers that are possible for the given compound. For example, when a compound consists of one stereogenic center a person skilled in the art will know that two enantiomers exist for this compound. He will also be able to draw, on paper, the absolute configuration of each enantiomer of the compound. However, possession of the racemate is not tantamount to possession of any one of the enantiomers (hence the patenability of the latter).

Moreover, the person skilled in the art expects that the enantiomers, if and when resolved, will have different physical properties and different chemical and biological activities, compared with the racemate and compared with each other.

However,it is not possible to know in advance, which of the two enantiomers (or whether both) will be active and, in fact, what is the activity of the each of the two[17] as compared with the activity of the racemate. As the Federal Circuit recently reminded us[18], "Thalidomide is a well-known example: one enantiomer is effective against morning sickness while the other causes birth defects".

As the person skilled in the art appreciates, different enantiomers may have different metabolic routes. They may have different metabolic routes in humans and in other animals. Enantiomers may metabolize one into the other in vivo. Enantiomers may also interact with one another in vivo. The enantiomers may each have *in vivo* activity that is different than their *in vitro* activity. It therefore follows that the racemate may be different from its enantiomers as regards its *in vivo* activity. Thus, a racemate should be viewed as a substance that is different from each of its enantiomers.

It is only with hindsight that one can refer to the racemate of citalopram as a "combination". It is only with the benefit of the invention of Lundbeck's invention, the resolved escitalopram, that one can argue that escitalopram was responsible for the activity of the racemate. How can one speak of "combination", when it is accepted that a person skilled in the art could not have resolved the enantiomers expected to be contained therein? Borrowing from Lindgren J's analogy[19] , if one can speak of the green color as a "combination" of yellow and blue, that may be so only after one is in the possession of the yellow and blue separately and decides to mix them, not when one first sees green and believes that it can be resolved to two basic colors[20].

The correct point of view is to identify the API of a drug containing a racemate as the racemate itself, which is a substance different from each of the enantiomers contained therein with respect to any type of property (physical, chemical and biological). The single enantiomer subsequently developed must be viewed as a separate and different API and thus deserves a new first registration in the Register of Medical Preparations, a separate patent and also a separate PTE.

[17] They may be both active, they may have a synergistic effect, one may inhibit the other, etc.[6] Section 64D(3) of the Patents Law.

[18] **Pfizer, Inc. vs. Ranbaxy Lab. Ltd.,** 457 F.3d 1284 (Fed. Cir. 2006).

[19] In **Alphapharm Pty Ltd v H Lundbeck A/S** [2008] FCA 559. An appeal is pending before the Full Court.

[20] At a time the person skilled in the art is not in possession of each of the separate basic colors.

(II) EX POST "COMBINATION" IS NOT A "MIRROR SITUATION"

Reverting to the Registrar's comment regarding a "mirror situation" referred to above, the situation discussed in the **Novartis** decision was that of a combination of two **known and available** APIs, Valsartan and Hydrochlorothiazide, combined as in a drug known as *Co-Diovan*(R). A PTE application based on the registration of *Co-Diovan*(R) was refused, on the basis that a combination of two **known** APIs does not constitute a new "substance". Such a situation cannot be compared with (and is certainly not a "mirror situation" of) the case of a racemate, before the invention of the resolved enantiomers.

It seems that the Registrar put too much emphasis on the (subsequently discovered) finding that escitalopram was "responsible" for the (favorable) activity of the racemate and that this caused him to disregard the racemic as an API in its own merit. This approach of the Registrar is too simplistic, and does not pay due heed to the complexities of science. Following are several examples for two different products which constitute different substances (or different APIs), notwithstanding what might be viewed as commonality of the "responsible" factor: native protein vs. recombinant protein; bacterially expressed (non-glycosylated) protein vs. CHO expressed (glycosylated) protein; antibody vs. humanized antibody, IgG vs. Fab fragment, cytokine vs. chimeric "combination" of the cytokine with a soluble protein of its receptor; protein vs. its metabolite, Yew extract vs. paclitaxel, and the list could go on and on.

(III) A RACEMATE IS NOT A SINGLE ENANTIOMERIC DRUG WITH "IMPURITIES"

The Registrar regarded the registration of the racemate as a previous registration of escitalopram with the remaining "ingredient" of the racemate being considered an "impurity". This is again a wrong approach[21]. As noted above, each of the racemate and the enantiomers are different active ingredients with different properties. Each of them may have an effect on the other.

It is therefore not surprising that a renowned scientist in the field warned, long ago (and only couple of years before the priority date of Lundbeck's enantiomer patent)[22] **that "to state bluntly that racemic drugs contain 50% impurity is a gross simplification"** and that **"Many factors, explicit and implicit, should be taken into account before reaching 'yes or no' answers … Such factors must be primarily scientific, and they require a wealth of pharmacodynamic and pharmacokinetic data which is not always available".**

Thus, an enantiomer (*e.g (R)*) may be viewed as an impurity only when the chiral drug substance is presented as a single enantiomeric drug (*e.g (L)*), but not when the chiral drug is presented as a racemate[23].

It is noteworthy that the Israeli Registrar chose not to address these scientific issues in his decision.

21 The Registrar referred to Case C-258/99 **BASF (Approximation of laws)** [2001] EUECJ C-258/99 [2001] ECR I-3643, [2001] EUECJ C-258/99, [2002] RPC 9. That case involved an application for SPC for a plant protection product. The patent invention was a manufacturing **process patent** (EP 0026847). BASF had previously registered a pesticide containing chloridazon as active substance, which was a mixture of two isomers having the proportion of 80/20, whereas the new pesticide also contained chloridazon as active substance, but this time with the two isomers in the mixture having the proportion of 90/10. This is a wholly different scenario than the case of a resolved enantiomer vs. a racemate. It is therefore not necessary to express an opinion on the BAFF decision.

22 **Bernard Testa,** *Trends Pharmacol. Sci.* 7:60-64, 1986**.**

23 Investigation of Chiral Active Substances (previous title: Clinical Investigation of Chiral Active Substances/ III/3501/91 [European Economic Community Website]

(IV) THE UNDERLYING LEGISLATIVE PURPOSE

It is not clear what is the perceived legislative purpose that the Registrar's decision tries to serve.

The legislative purpose of the PTE scheme is to alleviate the damage suffered by owners' new inventions, who are unable to commercialize their invention due to regulatory requirements.

The application date of the escitalopram patent[24] is 30 May 1989. *Cipralex*® was registered by the Ministry of Health thirteen years later, in 2002. The Patentee suffered a substantial delay. Moreover, Lundbeck was found entitled to a valid patent for the (*S*)-enantiomer as a new **product** (not for a process for manufacturing same, not for a new formulation, not for a new indication, but for a new product)[25]. Cipralex was required to undergo clinical development and registration process. The Ministry of Health deems Lundbeck's new product a **New Chemical Entity**[26].

What is, therefore, the alleged legislative that justifies the interpretation proffered by the Registrar, to deny PTE protection in such circumstances? The Registrar's decision does not explain.

It should be noted, however, that the Opponents argued that the hurdles faced by a manufacturer of a single enantiomer drug desiring to obtain a marketing approval are insignificant, when the racemate drug was already registered. The Opponents also argued that in the case at hand, all that Lundbeck was required to do was "to conduct one single trial".

The Registrar did not make a determination in this regard (although he apparently cast some doubt on the level of effort that Lundbeck invested.

To be sure, because a racemate and its enantiomers are different substances, and because it is not possible to know, **in advance**, what is the "contribution" of each enantiomer to the activity of the racemate as a substance, the health authorities view the racemate and the enantiomer as different APIs. Thus, "The development of a single enantiomer as a new active substance requires the same full preclinical documentation as any other new active substance" and "Development of a single enantiomer from an approved racemate: 'Chiral switching" represents one of the most common scenarios today. ….. In principle this is equivalent to the development of a new active substance requiring a complete new application."[27]. Admittedly, in the case of a chiral switch from a racemate to a single enantiomer, the sponsor is entitled to conduct "bridging studies", which, if successful, may entitle the sponsor to rely on studies conducted with the racemate as an API. However, for reason already mentioned, success is not predictable and certainly not guaranteed.

[24] No. 90465

[25] An invention directed to a new resolved enantiomer is entitled to patent protection as a product of its own, and not only as a process. See Lord Hoffman's judgment (sitting in the English Court of Appeal) in **H. Lundbeck A/S v Generics (UK) Ltd. & Ors** [2008] EWCA Civ 311, 2008 RPC 437. Approved by the House of Lords - **Generics (UK) Limited and others v H Lundbeck A/S** [2009] UKHL 12.

[26] The classification of an API as a New Chemical Entity for the purpose of Marketing Exclusivity (which is dependent on the novelty of the **active moiety** of the API) is not necessary for the conclusion that the new compound is a new "Substance". However, when the MoH determines that that the API of drug II is an NCE, such determination cannot be overlooked and it is inappropriate to hold that the API of a previous drug I is the same.

[27] R.R. Shah and S.K. Branch, "**Regulatory Requirements for the Development of Chirally Active Drugs**", at p. 389 and at p. 391(Chapter 16 in Handbook of Experimental Pharmacology, Volume 153, Editor-in-Chief: K. Starke, Freiburg i. Br.). It is noteworthy that the "**development of a nonracemic mixture from an approved racemate or single enantiomer**" is viewed differently – "**In principle, a tailored (nonracemic or nonequimolar) mixture of enantiomers can be viewed as an approach towards the optimization of a pharmacotherapeutic profile**" (ibid, p. 393).

Thus, "the extent of bridging studies should be defined **on a case-by-case basis**"[28] It is wrong to hold, as a general rule, that because the regulatory delay in cases of chiral switch **may be** shorter, PTE protection should not be available. Such general rule is, again, tainted with hindsight. The proper vantage point is *ex ante* and not *ex post* [29].

The proportionate treatment for this consideration is through the duration of the PTE Order. One must remember that the scope of protection afforded by a PTE is commensurate with the Patentee's contribution and delay suffered. A PTE will protect only the API of the registered drug and if the delay was shorter, the duration of the PTE Order will be shorter. It is a telling fact, that

(V) A MARKETING APPROVAL FOR A RACEMIC DRUG DOES NOT ALLOW MARKETING A DRUG CONTAINING THE SINGLE ENANTIOMER AS AN API

As a matter of interpretation of the Israeli Patents Law, it seems that the Registrar confused two separate conditions in reaching his, in our opinion, erroneous conclusion. As noted above, Section 64D(2) of the Patents Law requires that drugs "containing" the API claimed in the patent must be registered in the Register of Medical Preparations. Even if one were to accept the conclusion that the registration of *Cipramil*® (the racemate) should be deemed as registration of a drug "containing" the *(S)*-enantiomer, this is irrelevant and under-conclusive.

This is because the previous registration of the *(S)*-enantiomer (*Cipralex*®) did **not** "***… allow the [(S)-enantiomer] to be used in Israel for medical purposes***" and therefore cannot be considered as the "***the first registration***" that allowed the use of the *(S)*-enantiomer for medical purposes in Israel, as required by Section 64D(3) of the Law[30]. In any event, it is submitted that the correct interpretation of the phrase "containing" in context is "containing as the API".

Otherwise, one could (erroneously) argue that a previous registration of a drug "containing" compound X as a carrier, prevents a PTE for a subsequent drug containing compound X as an API. In the case at hand, it is clear that the Ministry of Health did not regard escitalopram as the API of Cipramil®.

(VI) THE CASE OF DIFFERENT SALTS

The Registrar noted, in passing, that under Israeli Patents Law different salts are deemed as the same "substance" of a registered drug. This statement requires separate discussion and detailed analysis and is not necessarily correct. If, as we believe, different salts constitute different substances having different physical, chemical and especially pharmacokinetic and pharmacodynamic properties, then escitalopram oxalate should be considered different than the racemic citalopram hydrobromide in addition to the difference conferred by the switch from the racemate to the single enantiomer.

[28] Investigation of Chiral Active Substances" (fn. 23 above), § 5.3

[29] R.R. Shah, "**Improving clinical Risk/Benefit Through Streochenisrty** ", at p. 389 and at p. 391(Chapter 17 in Handbook of Experimental Pharmacology, supra, at p.420

[30] The Registration of the racemate cannot be viewed as an authorization to place escitalopram on the market (even though it is "contained" in the mixture). Having regard to the proper context of Section 64D(3) and the regulatory scheme of registration of drugs, it is improper and wrong to regard the registration of citalopram hydrobromide as registration of escitalopram oxalate. Thus, in **Generics (UK) Ltd. v Daiichi Pharmaceutical Co Ltd. & Anor** [2008] EWHC 2413 (Pat) rightfully concluded that an earlier authorization to place *ofloxacin* on the market cannot be regarded as an authorization to place *levofloxacin* (the (-) enantiomer of a racemic compound called ofloxacin) on the market.

(VI) LUNDBECK'S APPEAL

An appeal by Lundbeck is pending before the District Court of Jerusalem. The Court allowed Lundbeck's request for accelerated hearing of the appeal and such hearing took place last week. That was because the patent will expire on 30th May, 2009, unless extended. The judgment is expected to be given before the expiry date of the Patent.

POSTSCCRIPT

On 8th April, the District Court of the Hague revoked the corresponding Dutch patent[30] and, consequently, also cancelled the SPC (No. 155) based on it. Because of the unique provisions of the Israeli Patents Law with respect to duration of PTE orders, the cancellation of the Dutch SPC may serve as a basis for a new and additional argument by the opponents that no PTE order should be granted in Israel. Whether or not such an argument is tenable[31] is a subject for separate discussion.

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[30] EP 0347066. The decision upheld the novelty of the invention, but held that the resolution was not inventive

[31] If in the affirmative, it will make Lundbeck's appeal superfluous. Nevertheless, because of the significant importance of the issue of availability of PTE for enantiomers, and because PTE litigation is often conduction in haste, due to the imminent expiry of the basic patent, a guiding judgment of the court is much needed.