Date	February 22, 2011	Court	Intellectual Property High Court, Second Division
Case number	2009 (Gyo-Ke) 10423–10429		
A case in which the court maintained the decision of the Japan Patent Office (JPO) dismissing the plaintiffs' requests for trials for invalidation of the registration of extension of the duration of a patent right			

References:Article 68-2 of the Patent Act

Summary of the Judgment

1. Background

This is a suit to seek rescission of the decision of the Japan Patent Office (JPO) dismissing requests for trials for invalidation of the registration of extension of the duration of a patent right. The point at issue in this case is whether or not the usage specified for the product which was the subject of the disposition which constituted the reason for the previous registration of extension made prior to the registration of extension in dispute is substantially the same as the usage relating to the registration of extension in dispute.

2. JPO decision

As the grounds for invalidation of the registration of extension in dispute, the requesters for trials for invalidation (plaintiffs) allege as follows: The usage specified for the product which was the subject of the disposition which constituted the reason for the previous registration of extension, that is, the usage relating to the previous approval, was "inhibition of the progression of symptoms of dementia in the case of the mild stage or medium stage of Alzheimer dementia" (previous usage), and the previous registration of extension was granted based on the disposition designated for this efficacy or effect. Meanwhile, the usage specified for the product which was the subject of the disposition, which was the reason for the registration of extension in dispute, is "inhibition of the progression of symptoms of dementia in the case of Alzheimer dementia (excluding inhibition of the progression of symptoms of dementia in the case of the mild stage or medium stage of Alzheimer dementia)" (in essence, "inhibition of the progression of symptoms of dementia in the case of the serious stage of Alzheimer dementia"). Thus, the specified usage relating to the previous registration and that relating to the registration in dispute are substantially the same. Therefore, the registration for extension in dispute was made in relation to an application for which a disposition designated by Cabinet Order under Article 67, paragraph (2) of the Patent Act is not deemed to have been necessary to obtain.

However, the previous usage, “inhibition of the progression of symptoms of dementia in the case of the mild stage or medium stage of Alzheimer dementia,” is not substantially the same as the usage specified for the registration of extension in dispute, “inhibition of the progression of symptoms of dementia in the case of Alzheimer dementia (excluding inhibition of the progression of symptoms of dementia in the case of the mild stage or medium stage of Alzheimer dementia)” (in essence, “inhibition of the progression of symptoms of dementia in the case of the serious stage of Alzheimer dementia”). Therefore, the registration for extension in dispute was not made in relation to an application for which it was not necessary to obtain a statutory approval intended to ensure the safety, etc. or any other disposition designated by Cabinet Order , for the working of the patented invention.

3. Court decision

The court found that there was no error in the JPO decision in terms of the conclusion to dismiss the plaintiffs’ requests for trials for invalidation of the registration for extension of the duration of the patent right, and dismissed the plaintiffs’ claim for rescission of the JPO decision. The holdings of the court can be summarized as follows.

The difference between the mild stage or medium stage of Alzheimer dementia and the serious stage of Alzheimer dementia can be understood as arising from the degree of seriousness of Alzheimer dementia, which is supposed to progress slowly and irreversibly. Even though donepezil hydrochloride has been confirmed to be effective and safe for inhibiting the progression of symptoms of the mild stage or medium stage of Alzheimer dementia, in order to prove the effectiveness and safety of this substance for the inhibition of the progression of symptoms of the serious stage of Alzheimer dementia, a more serious case, it seems that clinical tests were required to be carried out by giving donepezil hydrochloride to patients suffering the serious stage of Alzheimer dementia, thereby confirming the effectiveness and safety of this substance in such a serious case as well.

The term “usage” generally means the “purpose of using something,” and when it comes to the “usage” of a pharmaceutical product, this term is construed to refer to the disease or symptoms, etc. for which the pharmaceutical product is to work and bring about its efficacy or effect. The sameness in usage should not be determined merely in form, from evidence such as the statement in the written approval for partial change to the approved matters for manufacturing and sale of pharmaceutical product, but

determination should be made on the basis of the content, by taking into consideration the pathologic conditions, pharmacologic actions, symptoms, etc. of the disease targeted by the pharmaceutical product relating to the previous approval and those relating to the approval in dispute. In this case, although the previous approval and the later approval in dispute have some features in common in that the targeted disease is Alzheimer dementia and the pharmacologic action is inhibition of acetylcholinesterase, if they differ in terms of the degree of seriousness of the targeted disease, and it is therefore necessary to carry out additional clinical tests in order to confirm the effectiveness and safety for the application to the more serious case of the disease, which had not been covered by the previous approval, such situation can be regarded as the case where it was necessary to obtain a statutory approval intended to ensure the safety, etc. or any other disposition designated by Cabinet Order for the working of the patented invention, and a difference can be found in terms of the usage arising from the degree of seriousness of the targeted disease.

Accordingly, there is no error in the JPO decision finding that, as discussed above, although the targeted disease may be the same, the usage covered by the previous approval, "inhibition of the progression of symptoms of dementia in the case of the mild stage or medium stage of Alzheimer dementia" and the usage covered by the approval in dispute, "inhibition of the progression of symptoms of dementia in the case of the serious stage of Alzheimer dementia," cannot be deemed to be substantially the same, and thereby dismissing the plaintiffs' requests for trials for invalidation of the registration of extension of the duration of the patent right.

Judgment rendered on February 22, 2011; the original was received on the same day; court clerk

2009 (Gyo-Ke) 10423, 10424, 10425, 10426, 10427, 10428, and 10429 Cases of Seeking Rescission of JPO Decisions

Date of conclusion of oral argument: February 1, 2011

Judgment

Plaintiff: Sawai Pharmaceutical Co., Ltd.

Plaintiff: Shiono Chemical Co., Ltd.

Plaintiff: *Taisho* Pharmaceutical Industries, Ltd.

Plaintiff: *Taiyo* Pharmaceutical Industry Co., Ltd.

Plaintiff: Towa Pharmaceutical Co., Ltd.

Plaintiff: Nichi-Iko Pharmaceutical Co., Ltd.

Plaintiff: Nihon Pharmaceutical Industry Co., Ltd.

Plaintiff: Yoshindo Inc.

Defendant: Eisai Co., Ltd.

Main text

The plaintiff's claim in each case shall be dismissed.

The plaintiffs shall bear the court costs.

Facts and reasons

No. 1 Judgment sought by the plaintiffs

The JPO decisions rendered on November 25, 2009 in relation to Invalidation Trial Nos. 2008-800238, 2008-800239, 2008-800240, 2008-800241, 2008-800242, 2008-800243, and 2008-800244 shall be rescinded.

(The case numbers in this lawsuit correspond to the aforementioned trial case numbers in order.)

No. 2 Outline of the case

This case is an action to seek rescission of JPO decisions that dismissed requests for a trial for invalidation of the registration of extension of the duration of a patent right (the "Registration of Extension"). The issue is whether the usage specified in relation to the subject of a disposition which was made prior to the Registration of Extension and constituted the reason for the Registration of Extension is substantially identical with the usage specified in relation to the subject of a disposition which constituted the reason for the Registration of Extension.

1. Developments in procedures at the JPO and approval under the Pharmaceutical Affairs Act

(1) Registration of Extension and requests for a trial for invalidation thereof

The defendant filed a patent application (Patent Application No. 1988-153852) for an invention titled "cyclic amine derivatives" on June 22, 1988, and received the registration of establishment of a patent right for the invention on November 7, 1996 as Patent No. 2578475 (the "Patent"; the number of claims is six).

The defendant filed applications for the registration of extension of the duration of the Patent (Nos. 2007-700111, 2007-700112, 2007-700113, 2007-700114, 2007-700115, 2007-700116, and 2007-700117) on November 22, 2007. For each of the aforementioned applications, the registration of extension of the duration of the patent right in question (the "Patent Right") for five years was made on June 25, 2008 (the Registration of Extension). In response to this, the plaintiffs filed requests for a trial for invalidation of the Registration of Extension on November 7, 2008.

The JPO numbered these requests in order of the aforementioned application numbers, as Invalidation Trial Nos. 2008-800238, 2008-800239, 2008-800240, 2008-800241, 2008-800242, 2008-800243, and 2008-800244. The JPO examined these cases, and then rendered a decision that "The request for a trial in question shall be dismissed" for all of them on November 25, 2009. The certified copies of the JPO decisions were served to the plaintiffs on December 7, 2009.

(2) Previous registration of extension

In relation to the Patent, an extension of the duration was registered on December 19, 2001, for the reason of approval (previous approval) (based on Patent Application No. 1999-700114; an extension of the duration for the period of 2 years, 11 months, and 12 days), deeming the usage specified in relation to the product subject to the approval to be "suppression of the progression of dementia symptoms in mild and moderate dementia of Alzheimer type" as alleged by the plaintiffs as the usage that is substantially identical with the one specified in relation to the subject of the approval which constituted the reason for the Registration of Extension.

(3) Disposition that constituted the reason for the Registration of Extension

The Registration of Extension was approved for the reason that it was necessary to obtain the disposition designated by Cabinet Order (Order for Enforcement of the Patent Act) in relation to the working of the invention pertaining to the Patent. The content of the relevant disposition designated by Cabinet Order is as follows (the "Approval").

• Title: Approval of partial changes to the matters concerning approval of manufacturing and sale of a medicine

• Approval Nos.:

21100AMZ00662000 for Application No. 700111

21100AMZ00663000 for Application No. 700112
21900AMX01197000 for Application No. 700113
21600AMZ00405000 for Application No. 700114
21600AMZ00406000 for Application No. 700115
21900AMX01198000 for Application No. 700116
21300AMZ00373000 for Application No. 700117
• Approval date: August 23, 2007
• Product subject to the disposition: Donepezil hydrochloride
• Usage specified in relation to the product subject to the disposition
Suppression of the progression of dementia symptoms in dementia of Alzheimer type (however, excluding suppression of the progression of dementia symptoms in mild and moderate dementia of Alzheimer type)
• Names of products sold
Aricept 3 mg tablet for Application No. 700111
Aricept 5 mg tablet for Application No. 700112
Aricept 10 mg tablet for Application No. 700113
Aricept D 3 mg tablet for Application No. 700114
Aricept D 5 mg tablet for Application No. 700115
Aricept D 10 mg tablet for Application No. 700116
Aricept fine granules 0.5% for Application No. 700117
2. Gist of the patented invention in question (the "Patented Invention"; statements in Claims 1 to 6)
[Claim 1] 1-benzyl-4-[5,6-dimethoxy-(1-indanone)-2-yl]methylpiperidine expressed by the following chemical formula or pharmacologically acceptable salts thereof (the chemical formula is omitted)
[Claim 2] An acetylcholinesterase inhibitor whose active ingredient is 1-benzyl-4-[5,6-dimethoxy-(1-indanone)-2-yl]methylpiperidine or pharmacologically acceptable salts thereof stated in Claim 1
[Claim 3] Curative or preventive medicines for various types of senile dementia whose active ingredient is 1-benzyl-4-[5,6-dimethoxy-(1-indanone)-2-yl]methylpiperidine or pharmacologically acceptable salts thereof stated in Claim 1
[Claim 4] Curative or preventive medicines stated in Claim 3 for which the various types of senile dementia are senile dementia of Alzheimer type
[Claim 5] A process for manufacturing 1-benzyl-4-[5,6-dimethoxy-(1-indanone)-2-yl]methylpiperidine or pharmacologically acceptable salts thereof stated in Claim 1, which is characterized by reducing

1-benzyl-4-[5,6-dimethoxy-(1-indanone)-2-ylidenylmethylpiperidine and carrying out a salt-forming reaction when necessary

[Claim 6] A process for manufacturing 1-benzyl-4-[5,6-dimethoxy-(1-indanone)-2-yl]methylpiperidine or pharmacologically acceptable salts thereof stated in Claim 1, which is characterized by reacting 1-benzyl-4-piperidinecarbaldehyde and 5,6-dimethoxy-1-indanone to obtain 1-benzyl-4-[5,6-dimethoxy-(1-indanone)-2-ylidenyl]methylpiperidine, then reducing it, and carrying out a salt-forming reaction when necessary

3. Gist of the reasons given in the JPO decisions

The demandants (plaintiffs) allege as follows as a ground for the invalidation of the Registration of Extension: The usage specified in relation to the product subject to a disposition (previous approval) that constituted the reason for the previous registration of extension of the duration is "suppression of the progression of dementia symptoms in mild and moderate dementia of Alzheimer type" (previous usage), and said registration of extension was approved based on the disposition designating such usage as efficacy and effect. In addition, the demandants allege as follows: The previous usage and "suppression of the progression of dementia symptoms in dementia of Alzheimer type (excluding suppression of the progression of dementia symptoms in mild and moderate dementia of Alzheimer type)" (substantially, "suppression of the progression of dementia symptoms in severe dementia of Alzheimer type"), which is the usage specified in relation to the product subject to a disposition (the "Approval") that constituted the reason for the Registration of Extension, are substantially identical with each other, and the Registration of Extension was made in relation to an application that falls under a case where a disposition designated by Cabinet Order as set forth in Article 67, paragraph (2) of the Patent Act is not recognized as having been necessary to obtain for the working of the Patented Invention.

However, "suppression of the progression of dementia symptoms in mild and moderate dementia of Alzheimer type," which is the previous usage, and "suppression of the progression of dementia symptoms in dementia of Alzheimer type (excluding suppression of the progression of dementia symptoms in mild and moderate dementia of Alzheimer type)" (substantially, "suppression of the progression of dementia symptoms in severe dementia of Alzheimer type"), which is the usage pertaining to the Registration of Extension, are not substantially identical with each other. Therefore, the Registration of Extension is not the one that was made in relation to an application that falls under the case where approvals prescribed by relevant Acts that are intended to

ensure the safety, etc. or any other disposition designated by Cabinet Order is not necessary to obtain for the working of the Patented Invention.

No. 3 Grounds for rescission of the JPO decisions as alleged by the plaintiffs

Regarding the provision in Article 67, paragraph (2) of the Patent Act "… disposition … is necessary to obtain for … the patented invention," granting of an approval prescribed in the Pharmaceutical Affairs Act should not be formally understood; and for a medicine that is subject to approval set forth in Article 14, paragraph (1) of the Pharmaceutical Affairs Act, a determination should be based on whether a disposition was necessary to obtain in relation to differences from two perspectives, that is, product (active ingredient) and usage (efficacy and effect). However, the JPO decisions contain an error in their determinations concerning the identity of usage between the Approval and the previous approval. Therefore, the JPO decisions should be rescinded as illegal.

(omitted)

No. 4 Court decision

1. Regarding dementia of Alzheimer type

(1) The following Documents A to E describe as follows in relation to the definition, causes, pathological condition (pathophysiology), symptoms, etc. of dementia of Alzheimer type.

A. Nanzando *Nanzando's Medical Dictionary, 19th Edition* (Exhibits Ko 29 and 40)

(A) "Dementia" section

The term "dementia" refers to the condition where intellectual power, memory, capacity for judgment, capacity to understand, abstraction capacity, language, capacity for action, cognition, faculty of orientation, feelings, motivation, characters, and various other mental functions, which were acquired in a person's developmental process, are impaired due to organic brain disorders (causative disease), and thereby, the person has become unable to perform independently in his or her daily/social life and maintain smooth personal relationships. (snip)

(B) "Dementia of Alzheimer type" section

A type of dementia of Alzheimer type that develops in the presenile period is named after Alzheimer, who first described it, and is called Alzheimer's disease. Another type that develops later in life is called senile dementia on the pattern of description that has been adopted since Pinel early in the 19th century, or senile dementia of Alzheimer type

(SDAT). These two types are collectively referred to as dementia of Alzheimer type. (snip)

(C) "Alzheimer's disease" section

A type of dementia of Alzheimer type that develops in the presenile period is named after Alzheimer, who first described it, and is called Alzheimer disease. Another type that develops later in life is called senile dementia of Alzheimer type (SDAT). These two types are collectively referred to as dementia of Alzheimer type. In the presenile period, the disease develops around the time when patients are in their late 40s or 50s. Later in life, the disease develops when patients are in their late 70s and thereafter. The dementia of Alzheimer type is a degenerative cerebral disease whose progression is as follows: The disorder of memory, disorder of motivation, disorder of judgment, aphasia, apraxia, agnosia, personality disorder, emotional disorder, mirror phenomenon, Klüver-Bucy syndrome, and other symptoms develop, which cause patients to fall into severe dementia; furthermore, epileptic seizure, muscle rigidity, and other nervous symptoms also develop; at last, patients show apallic syndrome and become bedridden, resulting in death. As pathological changes in the brain, there are senile plaques (deposition of amyloid β protein), Alzheimer's neurofibrillary tangles (neurofibrillary tangles), and loss of nerve cells. Such pathological changes advance more as the disease situation proceeds, causing marked brain atrophy (→cerebral atrophy). Pathological changes are strong in the hippocampus in the medial-temporal lobe and at the joint of the medial-temporal, parietal, and occipital lobes. As the pathological condition, abnormal and early deposition of amyloid β protein (→β-protein) and accumulation of phosphorylated tau protein in nerve cells are important. In addition, it has been revealed that the abnormal phenomenon of acetylcholine and other neurotransmitters exist behind the disease. (snip)

B. Translation supervised by Michio Toru, at el., *The ICD-10 Classification of Mental and Behavioural Disorders—Clinical descriptions and diagnostic guidelines—newly-revised version*, Igaku-Shoin Ltd., "F00 Dementia in Alzheimer's disease" in "F0 Organic, including symptomatic, mental disorders," pp. 58-59 (Exhibit Ko 32)

Alzheimer's disease is a primary degenerative cerebral disease of unknown etiology, with characteristic neuropathological and neurochemical features. It is usually insidious in onset and develops slowly but steadily over a period of years. This period can be as short as 2 or 3 years, but can occasionally be considerably longer. … (snip) …

There are characteristic changes in the brain: a marked reduction in the population of neurons, particularly in the hippocampus, substantia innominata, locus ceruleus, and

temporoparietal and frontal cortex; appearance of neurofibrillary tangles made of paired helical filaments; neuritic (argentophil) plaques, which consist largely of amyloid and show a definite progression in their development (although plaques without amyloid are also known to exist); and granulovacuolar bodies. Neurochemical changes have also been found, including a marked reduction in the enzyme choline acetyltransferase, in acetylcholine itself, and in other neurotransmitters and neuromodulators.

As originally described, the clinical features are accompanied by the above brain changes. However, it now appears that the two do not always progress in parallel: one may be indisputably present with only minimal evidence of the other. Nevertheless, the clinical features of Alzheimer's disease are such that it is often possible to make a presumptive diagnosis on clinical grounds alone. Dementia in Alzheimer's disease is at present irreversible. (snip)

C. Chikayuki Ochiai, *Nōshinkeishikkan vijuaru bukku* (Visual book of cranial nerve diseases), Gakken Medical Shujunsha Co., Ltd., p. 196 (Exhibit Ko 38-1)

Unit 1 Dementia: Alzheimer's disease

• Disease concept

The disease presents with slowly progressive memory disorder, and it is the biggest culprit in causing senile dementing illness. The parietal lobe and the medial-temporal lobe, including the hippocampus, are vulnerable. In terms of pathological histology, the disease is characterized by the *appearance* of senile plaques where amyloid β protein aggregates, the *appearance* of neurofibrillary tangles (NFT) that consist of abnormally phosphorylated tau protein, and the dropout of acetylcholinergic cells (disappearance or decrease).

• Pathological condition

● Amyloid hypothesis: The pathological condition is anchored by the appearance of senile plaques (SP) that consist of an abnormal protein called amyloid β (Aβ) protein.

● In addition, brain cells are rapidly reduced due to the appearance of degenerated neurofibrils and remarkable dropout of acetylcholinergic nerve cells, and the brain shrinks, causing mental deterioration and personality disintegration.

• Disease situation and clinical findings

● Mild cognitive impairment (MCI) as a precursor state

● Anchored by a slowly progressive disorder of recent memory and time-and-place disorientation

● Personality/behavioral changes and psychological symptoms appear at a later stage. These are called behavioral and psychological symptoms of dementia (BPSD).

• Test, diagnosis, and classification

● Clinical diagnosis is based on the patient's clinical history and clinical presentation.
● Neuropsychological test
● Imaging tests (MRI, SPECT, FDG-PET, and amyloid PET)
● Cerebrospinal fluid biomarkers (amyloid β42 protein, phosphorylated tau protein, etc.)
● A definite diagnosis is made based on a pathological tissue at autopsy. (snip)

D. Translation supervised by Takashi Asada, *Alzheimer's at your fingertips: the comprehensive dementia reference book for the year 2000*, Igaku-Shoin Ltd., pp. 12-13 (Exhibit Ko 31)

Q 17 How does Alzheimer's disease usually progress? Is its progression usually similar between patients?

The progression of Alzheimer's disease is as different as fingerprints. The rate of progression of symptoms varies. The symptoms indicated below are representative examples, but they are not necessarily seen. Basically, Alzheimer's disease progresses slowly.

Here, for descriptive purposes, the progression is classified into three periods: "early," "middle," and "late." In actuality, however, the progression cannot be properly classified in this manner. This is absolutely a rough classification, but it should serve as a reference when caretakers recognize problems and make plans for care in the future.

[Symptoms in the early period]

The early symptoms of Alzheimer's disease are easy to overlook, and even doctors and patients' friends and relatives may deem such symptoms as those attributable to the patients' age. As the disease develops very slowly, it is not easy to exactly determine the time when the disease originally developed. Specifically, the following symptoms appear.

• Problems in terms of language
• Disorder of memory, in particular, problems in the capacity to register (to learn new things)
• A weak sense of time
• Getting lost in a place that the patient is supposed to know

… (snip) …

[Symptoms in the middle period]

The problems become clearer as the disease progresses, and the disease causes problems in various aspects of daily living.

• Forgetfulness becomes prominent, and it is noticeable, in particular, in relation to recent events and people's names.

• The patient cannot live independently without problems.
• The patient cannot cook, do housecleaning, and shop.
• The patient becomes very dependent.
• The patient requires assistance in relation to elimination, bathing, and personal hygiene.
• The patient also requires assistance getting dressed and undressed.
• The patient develops further difficulty in having conversations.
• The patient wanders and goes missing.
… (snip) …
[Symptoms in the late period]

At this time, the patient becomes bedridden, and requires full nursing care.

E. Edited under the supervision of Toshio Otsuka and Akira Honma, *Assessment manual of intellectual function for the demented elderly*, World Planning Co. Ltd., "Functional Assessment Staging (FAST)," pp. 59-64 (Exhibit Ko 44)

According to this document (Exhibit Ko 44), Functional Assessment Staging (FAST) is a classification of dementia of Alzheimer type according to the severity of impairment in ADL (note in this judgment: ability to perform activities of daily life). It is an intellectual function test that is intended to comprehensively assess the subject functions for daily activities to determine the severity of dementia, in particular, dementia of Alzheimer type. In FAST, dementia of Alzheimer type is classified into seven stages in total, including normal aging. The clinical diagnosis and characteristics under FAST for patients at Stage 4 or higher are as follows.

• Stage 4 (Moderate cognitive decline)

The clinical diagnosis is "mild dementia of Alzheimer type." The characteristic under FAST is "having difficulties performing tasks, such as planning dinner for guests, handling personal finances, and shopping."

• Stage 5 (Moderately sever cognitive decline)

The clinical diagnosis is "moderate dementia of Alzheimer type." The characteristic under FAST is "being unable to choose and wear proper clothing without assistance and sometimes requiring conciliatory persuasion for bathing."

• Stage 6 (Severe cognitive decline)

The clinical diagnosis is "moderately severe dementia of Alzheimer type." The characteristics under FAST are "[a] improper clothing, [b] requiring assistance for bathing and being unwilling to bathe, [c] becoming unable to flush the toilet, [d] urinary incontinence, and [e] fecal incontinence."

• Stage 7 (Very severe cognitive decline)

The clinical diagnosis is "severe dementia of Alzheimer type." The characteristics under FAST are "[a] decline in language function limited to approximately six words at most, [b] becoming able to understand only a single word, [c] loss of the ambulatory ability, [d] loss of the ability to sit up, [e] loss of the ability to smile, and [f] stupor and coma."

(2) According to the statements in the aforementioned documents, Alzheimer's disease is a primary degenerative cerebral disease of unknown etiology, and is one of the diseases that cause dementia. As the pathological changes of the brain, there are the appearance of senile plaques (SP) that consist of an abnormal protein called amyloid β (Aβ) protein, the *appearance* of degenerated neurofibrils, and shrinkage of the brain due to a rapid decrease in the number of brain cells caused by a remarkable dropout of acetylcholinergic nerve cells. The dementia of Alzheimer type progresses slowly and irreversibly, and is classified into stages, specifically, early, middle, and late stages, or mild, moderate, and severe stages.

2. Regarding differences between mild and moderate dementia of Alzheimer type and severe dementia of Alzheimer type in the previous approval and the Approval

The JPO ruled, on the grounds of a difference in the pathological condition, that "mild and moderate dementia of Alzheimer type" and "severe dementia of Alzheimer type" are substantially different diseases that can be distinguished based on the pathological condition (each written JPO decision, pages 13 to 14). The defendant alleges the same effect.

However, as mentioned above, various medical books are recognized as handling Alzheimer's disease and dementia of Alzheimer type as one disease and classifying it into stages, specifically, early, middle, and late stages, or mild, moderate, and severe stages.

In addition, the following is stated in the written application for approval of partial changes to the matters concerning approval of manufacturing and sale of a medicine pertaining to the Approval (Exhibit Ko 2-4) as the content and reasons of the changes: "This application is intended to change 'efficacy and effect' to make it possible to use the medicine for suppression of the progression of dementia symptoms in overall dementia of Alzheimer type from a mild-to-severe one, irrespective of the severity, based on the clinical trials on patients with severe dementia of Alzheimer type. Along with that, this application is filed to seek approval of partial changes, which are intended to change "dosage and administration," increasing it to 10 mg per day for patients with severe dementia of Alzheimer type." Moreover, the following is stated in the Review Report (Exhibit Ko 3) on the application for approval pertaining to the

Approval (the "Application for Approval"): "In 231 trials conducted in Japan targeting Japanese patients with severe dementia of Alzheimer type, the Drug showed its effectiveness in both of the two major assessment items: SIB and CIBIC plus. Therefore, the PMDA's determination that the Drug is positioned as a drug that suppresses the progression of dementia symptoms, irrespective of the severity of the disease, including mild and moderate dementia of Alzheimer type, for which approval has already been made, was supported in the Expert Discussion" (page 33). In light of these statements, the defendant and the review authority (Pharmaceuticals and Medical Devices Agency: PMDA) are recognized as classifying dementia of Alzheimer type into mild, moderate, and severe stages, depending on the severity thereof.

In that case, it is reasonable to recognize that, in the previous approval and the Approval, "mild and moderate dementia of Alzheimer type" and "severe dementia of Alzheimer type" are the classifications of one disease, dementia of Alzheimer type, depending on the severity thereof, rather than referring to substantially different diseases.

According to pages 10 and 16 of the Review Report pertaining to the Application for Approval (Exhibit Ko 3), the standard for choosing trial subjects in the clinical trials conducted in Japan and abroad for the purpose of obtaining the Approval is as follows: The trial subjects should be patients aged 50 or older who fulfill the conditions, such as those being at FAST Stage 6 or higher as of the starting date of observation (four weeks before administration) and those whose Mini-Mental State Examination (MMSE) score is 1 to 12 as of the starting date of observation. In light of this, severe dementia of Alzheimer type in the Approval is considered to be dementia of Alzheimer type that fulfills the condition of being at FAST Stage 6 or higher. More specifically, according to the aforementioned classification standard of FAST, in the case of mild dementia of Alzheimer type, the patient has no problem performing the basic activities of daily life, such as changing clothing, elimination, and eating; but in the case of moderate dementia of Alzheimer type, the patient comes to have problems performing basic activities. In the case of moderately severe or severe dementia of Alzheimer type, the patient is recognized as having problems performing many basic activities of daily life and as being in the state that he/she is unable to perform daily activities without assistance. Therefore, FAST is recognized as being premised on the fact that there are differences between mild and moderate dementia of Alzheimer type and severe dementia of Alzheimer type on this point.

3. Regarding the pharmacological action of the medicine in question (the "Medicine") in the previous approval and the Approval

(1) The following is stated in the report and document of Exhibits Ko 3 and 6 below.

A. On page 6 of the "Review Report" (dated July 10, 2007) prepared by the PMDA upon the Application for Approval (Exhibit Ko 3)

In adding efficacy this time, the applicant alleges that this medicine has an effect on dementia of Alzheimer type of various levels of severity, including severe level, in clinical practice for reasons such as that this medicine inhibits AChE in the brain ex vivo in a dose-dependent manner within the wide dose range (Application Material at the Time of Previous Approval E-1-2), that the severity of dementia of Alzheimer type and the degree of cholinergic nerve disorder are well correlated with each other in terms of clinical practice (J. Neurochem 64: 749-760, 1995), and that cholinergic nerve activity remains to a satisfactory extent even in the case of severe dementia of Alzheimer type (JAMA 281: 1401-1406, 1999).

The PMDA requested the applicant to pharmacologically consider the reason that no clinical effect can be obtained in the case of severe dementia of Alzheimer type unless a higher dosage of this medicine is administered than in the case of mild and medium dementia of Alzheimer type, as well as the degree (limit) of cholinergic nerve disorder on which this medicine is considered to show its effectiveness, taking into account that the severity of dementia of Alzheimer type is correlated with AChE activity and that AChE activity declines as dementia of Alzheimer type becomes more severe, as explained by the applicant by citing the aforementioned published paper.

In response, the applicant answered as follows. It is inferred that as dementia of Alzheimer type becomes more severe, the dropout of cholinergic nerve occurs more frequently and the level of acetylcholine (hereinafter referred to as "ACh") in the synaptic cleft decreases. Therefore, it is considered necessary to increase the level of ACh in the synaptic cleft by strongly inhibiting AChE with the use of a higher dosage of AChE inhibitor. …

B. On pages 13 and 21 of "Drug Interview Form (revised in July 2008) [revised 17th edition]" of the defendant and Pfizer Japan Inc. (Exhibit Ko 6)

• V. Item on medical treatment

1. Efficacy or effect

(2) Precautions in relation to efficacy or effect

2) There have been no results showing that this drug suppresses the progression of the pathological condition of dementia of Alzheimer type itself.

(Explanation)

This drug is an acetylcholinesterase inhibitor, and is intended to alleviate the symptoms of dementia of Alzheimer type through activation of the cholinergic nervous

system. It is not a drug that suppresses the progression of the pathological condition itself.

• VI. Item on pharmacology

2. Pharmacological action

(1) Action site and mechanism

A remarkable disorder of the brain's cholinergic nervous system is recognized in dementia of Alzheimer type. This drug increases the amount of acetylcholine (ACh) in the brain by inhibiting acetylcholinesterase (AChE), which is an acetylcholine-degrading enzyme, in a reversible fashion, thereby activating the brain's cholinergic nervous system.

(2) According to the statements in the aforementioned document, the pharmacological action of the Medicine is the same in terms of both mild and moderate dementia of Alzheimer type and severe dementia of Alzheimer type in that the amount of acetylcholine (ACh) in the brain is increased by inhibiting acetylcholinesterase (AChE), which is an acetylcholine-degrading enzyme, in a reversible fashion, thereby activating the brain's cholinergic nervous system. It is recognized that the dosage is increased to 10 mg per day for patients with severe dementia of Alzheimer type for the purpose of strongly inhibiting AChE with the use of a higher dosage of AChE inhibitor.

4. Background to the Approval

(1) The following is stated in the aforementioned Review Report (Exhibit Ko 3).

A. On page 1 of the Review Report: "Notes"

[Brand name]

[i] Aricept 3 mg tablet, [ii] Aricept 5 mg tablet, [iii] Aricept 10 mg tablet, [iv] Aricept D 3 mg tablet, [v] Aricept D 5 mg tablet, [vi] Aricept D 10 mg tablet, and [vii] Aricept fine granules 0.5%

[Non-proprietary name]

Donepezil hydrochloride

… (snip) …

[Application classification]

[iii][vi]: 1-(4), (6), (7)-2 Drug pertaining to addition of new efficacy, dosage, and dosage form (not those that are being re-reviewed)

[i][ii][iv][v][vii]: 1-(4), (6) Drug with new efficacy and dosage

B. On page 3 of the Review Report: "II. 1. Origin or history of discovery and usage conditions in foreign countries, etc." in Review Report (1)

Donepezil hydrochloride (hereinafter referred to as the "Drug") is an acetylcholinesterase (hereinafter referred to as "AChE") inhibitor developed by Eisai

Co., Ltd. In Japan, "Aricept 3 mg tablet" and "Aricept 5 mg tablet" were approved on October 8, 1999, "Aricept fine granules 0.5%" was approved on March 15, 2001, and "Aricept D 3 mg tablet" and "Aricept D 5 mg tablet" were approved on February 26, 2004, designating "suppression of the progression of dementia symptoms in mild and moderate dementia of Alzheimer type" as the efficacy and effect. This time, approval was made for the addition of dosage forms, "Aricept 10 mg tablet" and "Aricept D 10 mg tablet," for the purpose of high-dose administration while designating "suppression of the progression of dementia symptoms in dementia of Alzheimer type," in which patients with severe dementia of Alzheimer type are added to the subject patients, as the efficacy and effect, based on the results of clinical trials, etc. targeting patients with severe dementia of Alzheimer type. Incidentally, as of this writing, no drug that has an efficacy and effect on severe dementia of Alzheimer type has been approved in Japan.

C. On pages 7 to 8 of the Review Report: Outline of the Review section in Review Report (1)

The PMDA considers as follows. If the efficacy subject to this application is recognized, the Drug is applied to dementia of Alzheimer type for mild to severe stages … a double dosage compared to the dosage in the past is administered to patients with severe dementia of Alzheimer type in which the pathological condition have progressed … there are concerns about a possible increase of adverse effects on safety.

D. On page 31 of the Review Report: "IV. Overall Evaluation" in Review Report (1)

As a result of consideration as above, the PMDA determined that administration of 10 mg per day of the Drug to patients with severe dementia of Alzheimer type is recognized as effective and that, in terms of safety, it is also possible to prevent major problems by appropriately increasing the dosage by going through the steps of administering 3 mg per day and 5 mg per day at the initial stage of administration. Although it is necessary to continue to collect information about the safety of administration of 10 mg per day, it is of significance to provide a drug that can be used for suppressing the progression of severe dementia of Alzheimer type in the domestic clinical sites for the first time. Therefore, the PMDA determined that this application can be approved. The PMDA will eventually determine reminders that become necessary due to this addition of efficacy and collection of information that is necessary after manufacturing and sale, etc. in light of discussions held in the Expert Discussion.

E. On page 33 of the Review Report: "3. Efficacy and Effect" in Review Report (2)

(i) Addition of efficacy for severe dementia of Alzheimer type

In 231 trials conducted in Japan targeting Japanese patients with severe dementia of Alzheimer type, the Drug showed effectiveness in both of the two major assessment

items, that is, SIB and CIBIC plus. Therefore, the PMDA's determination that the Drug is positioned as a drug that suppresses the progression of dementia symptoms, irrespective of the severity thereof, including mild and moderate dementia of Alzheimer type, for which approval has already been made, was supported in the Expert Discussion.

(2) According to the statements in the aforementioned Review Report, in Japan, there were the following situations prior to the Approval: [i] Donepezil hydrochloride had been approved while designating suppression of the progression of dementia symptoms in mild and moderate dementia of Alzheimer type as the efficacy and effect, but no approval had been given to not only donepezil hydrochloride but also any other drugs while designating suppression of the progression of dementia symptoms in severe dementia of Alzheimer type as the efficacy and effect; [ii] Then, the Application for Approval was made in relation to donepezil hydrochloride while designating "suppression of the progression of dementia symptoms in dementia of Alzheimer type," which also includes patients with severe dementia of Alzheimer type in the subject patients, based on the results of clinical trials, etc. on donepezil hydrochloride targeting patients with severe dementia of Alzheimer type; [iii] This application was reviewed by the PMDA, and the PMDA expressed safety concerns about the administration of a double dosage compared to the dosage in the past for severe dementia of Alzheimer type; however, it concluded that approval can be given for the Application for Approval because it is possible to prevent major problems by appropriately increasing the dosage by going through the steps of administering 3 mg per day and 5 mg per day at the initial stage of administration and because it is of significance to provide a drug that can be used for suppressing the progression of severe dementia of Alzheimer type in the domestic clinical sites for the first time; [iv] Donepezil hydrochloride showed its effectiveness in domestic clinical trials targeting Japanese patients with severe dementia of Alzheimer type, and therefore, the Expert Discussion supported positioning donepezil hydrochloride as a drug that suppresses the progression of dementia symptoms, irrespective of the severity of the disease; [v] Therefore, the PMDA made the final judgment that there is no problem with giving approval for the Application for Approval.

5. Regarding identity between the usage in the previous approval and the usage in the Approval

According to the aforementioned finding, the difference between mild and moderate dementia of Alzheimer type and severe dementia of Alzheimer type is understood as a difference based on the severity of dementia of Alzheimer type that progresses slowly

and irreversibly. Even if donepezil hydrochloride is confirmed to be safe and effective for suppressing the progression of the symptoms of mild and moderate dementia of Alzheimer type, it is recognized as having been necessary to conduct clinical trials to confirm the effectiveness and safety of donepezil hydrochloride by administering it to patients with severe dementia of Alzheimer type in order to conclude that donepezil hydrochloride is safe and effective for suppressing the progression of severe dementia of Alzheimer type, which is more severe than mild and moderate dementia of Alzheimer type.

Then, the term "usage" means "way of use and application." The "usage" of a medicine is understood as meaning diseases and symptoms, etc. on which the medicine acts to produce its efficacy or effect. The identity in "usage" is not formally determined based on the statements in a written approval of partial changes to the matters concerning approval of manufacturing and sale of a medicine, etc., but should be substantially determined in consideration of the pathological condition (pathophysiology), pharmacological action, symptoms, etc. of the disease subject to the application of the medicine pertaining to the previous approval and the Approval. Similarly to this case, if separate clinical trials are necessary to confirm safety and effectiveness on more severe dementia, which is not covered by the previous approval, because the previous approval and the subsequent approval differ in the severity of the subject disease though they are the same in that the subject disease is dementia of Alzheimer type and that the pharmacological action is the inhibition of acetylcholinesterase, the case should be considered a case where approvals prescribed by relevant Acts that are intended to ensure the safety, etc. or any other disposition designated by Cabinet Order is necessary to obtain for the working of a patented invention, and differences in usage based on the severity of the disease should be recognized.

Therefore, in this case, as held above, the JPO decisions that dismissed the request for a trial for invalidation of the registration of extension of the duration by ruling as follows contain no error in the conclusion of their determinations: Even if the previous approval and the Approval are recognized as being given for the same disease, in terms of usage, the usage in the previous approval, "suppression of the progression of dementia symptoms in mild and moderate dementia of Alzheimer type," and the usage in the Approval, "suppression of the progression of dementia symptoms in severe dementia of Alzheimer type," cannot be considered to be substantially identical with each other.

6. Regarding the adverse effects alleged by the plaintiffs

With regard to distinction between "mild and moderate dementia of Alzheimer type" and "severe dementia of Alzheimer type" in the previous approval and the Approval, dementia of Alzheimer type at FAST Stage 6 or higher is supposed to be considered to be "severe dementia of Alzheimer type," taking into account the background to the Approval as mentioned above. However, neither clear definition nor standard is indicated in the previous approval and the Approval in relation to the severity of dementia of Alzheimer type, specifically, "mild," "moderate," and "severe," and FAST is merely one of the determination standards for classifying dementia of Alzheimer type based on the disease stage and severity thereof (Exhibit Ko 44). In light of these facts, it is not necessarily possible to consider that there is no reason for the allegation that the situation where a generic drug can be used for mild and moderate dementia of Alzheimer type but cannot be used for severe dementia of Alzheimer type causes confusion in medical practice.

However, this allegation itself is hypothetical, and as mentioned above, dementia of Alzheimer type can be classified into stages, such as "early," "middle," and "late" stages, or "mild," "moderate," and "severe" stages, though the standard for such classification is not unambiguously clear. In light of all the evidence in question, the defendant is not recognized as having especially extracted only part of the disease stages of dementia of Alzheimer type (severe dementia of Alzheimer type) for descriptive purposes and conducted clinical trials, etc. separately from those for mild and moderate dementia of Alzheimer type in order to extend the duration of the Patent Right. In addition, if previous approval and subsequent approval differ in the severity of the subject disease and separate clinical trials are necessary to confirm safety and effectiveness with regard to the disease at a more severe stage, which is not covered by the previous approval, the duration of the patent is eroded due to the period spent for the clinical trials, etc., and such case is considered to fall under the case where approvals prescribed by relevant Acts that are intended to ensure the safety, etc. or any other disposition designated by Cabinet Order is necessary to obtain for the working of a patented invention, as mentioned above.

In that case, it cannot be said that the usage in the previous approval and that in the Approval are the same on the grounds of the likelihood of causing confusion in medical practice and the fact that the previous approval and the Approval pertain to the same usage in that the subject disease is dementia of Alzheimer type, which are pointed out by the plaintiffs.

No. 5 Conclusion

On these bases, there is no reason for the ground for rescission as alleged by the plaintiffs.

Therefore, the plaintiffs' claim shall be dismissed, and the judgment shall be rendered in the form of the main text.

Intellectual Property High Court, Second Division

Presiding judge: SHIOTSUKI Shuhei

Judge: MANABE Tomoko

Judge: TANABE Minoru