IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

HOSPIRA, INC., Plaintiff, v. FRESENIUS KABI USA, LLC, Defendant.	Civil Action No. 1:16-cv-00651 Hon. Judge Rebecca R. Pallmeyer

HOSPIRA'S RESPONSIVE CLAIM CONSTRUCTION BRIEF

The parties dispute the construction of three terms, two of which lie at the center of the claimed invention: "ready to use" and "sealed glass container." As discussed below, these features solved a need in the art for a safer and more convenient dexmedetomidine drug product. While Hospira's constructions of the terms accurately define the invention, Fresenius Kabi has proposed incorrect constructions that are based on an oversimplified view of the claimed subject matter.

I. The Claimed Invention

The four patents-in-suit[1] relate to ready-to-use compositions of the sedative dexmedetomidine. (*E.g.*, JA-2 at 1:5-10.) Hospira's predecessor, Abbott Laboratories, began selling dexmedetomidine under the name Precedex™ in 1999. (*See* JA-249-61.) However, the 100 microgram per milliliter (µg/mL) concentration of dexmedetomidine in Precedex™ was too

[1] The patents are U.S. Patent Nos. 8,242,158 ("the '158 patent"); 8,338,470 ("the '470 patent"); 8,455,527 ("the '527 patent"); and 8,648,106 ("the '106 patent"). They share a common specification.

concentrated to administer to patients. (JA-2 at 1:48-49.) Medical personnel had to dilute Precedex™ to 4 µg/mL before administering it to the patient. (*Id.*; JA-62.) Upon dilution, the composition would be administered to the patient within twenty-four hours to prevent any loss of potency. (*E.g.*, JA-373 (FDA Memorandum noting that "[t]he drug product is prepared for use by diluting it with sterile 0.9% sodium chloride solution for injection after which it is stable for 24 hours").)

This dilution step presented problems. (*E.g.*, JA-2 at 1:50-53.) The need to have a medical professional perform dilution at the time of administration was an inconvenience that entailed added cost. (*E.g.*, *id.*) It also posed safety concerns, as errors made in preparing the diluted composition would result in a patient receiving dexmedetomidine at the wrong concentration. (*Id.*) There was also a risk of contamination during dilution. (*Id.*) However, because it was believed that diluted dexmedetomidine was stable for no more than twenty-four hours, Precedex™ continued to be sold only in its concentrated form for well over a decade. (*See, e.g.*, JA-2 at 1:48-49.)

The inventors set out to solve these problems by creating a ready-to-use formulation that eliminated the dilution step. (JA-2 – JA-3 at 1:53-65, 2:62-3:3.) They faced a major challenge due to the diluted composition's very low dexmedetomidine concentration. Specifically, at 4 µg/mL, even small changes in dexmedetomidine potency would amount to a significant loss in relative terms. (*E.g.*, JA-12 at 21:59-61.) Thus, the inventors needed to develop a diluted, low concentration dexmedetomidine formulation that maintained its potency for an extended period. (JA-2 at 2:62-66.) The inventors experimented with numerous different formulations, trying various buffers, pH levels, additives, and packaging materials. (*See* JA-8 – JA-9.) After months

of stability testing, they discovered that glass packaging exhibited superior stability relative to the other packaging materials tested. (*E.g.*, JA-8 at Example 1.)

The inventors' work was still not done. They then had to ensure the shelf-life stability and sterility of the product by developing a sealed system. (*See* JA-4 at 5:59-65; JA-6 at 9:1-7.) They tested several closure systems for integrity without success before finding a stopper that was compatible with the glass container and formed a "sealed glass container." (*See* JA-11 – JA-12 at 20:45-21:16.)

Through their work, the inventors developed the claimed invention—a "ready-to-use" dexmedetomidine formulation in a "sealed glass container." Claim 1 of the '158 patent is exemplary:

> A ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 µg/mL disposed within a sealed glass container.

(JA-14 at Claim 1.) This inventive composition exhibited prolonged stability, allowing it to be kept on the shelf until needed, as claimed in the '106 patent:

> A ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof disposed within a sealed glass container, wherein the liquid pharmaceutical composition when stored in the glass container for at least five months exhibits no more than about 2% decrease in the concentration of dexmedetomidine.

(JA-57 at Claim 1.)

The benefits of the claimed invention are manifest. The embodiment of the claimed subject matter, Precedex™ Premix, enjoys a majority share of the dexmedetomidine market and commands a premium price. Indeed, even though Fresenius Kabi currently sells a generic

version of the concentrated version of Precedex™, it is now seeking approval to sell the superior ready-to-use product prior to the expiry of the patents-in-suit.

II. Proposed Constructions

a. "ready to use" (all asserted claims)

Hospira's Proposed Construction	*Fresenius Kabi's Proposed Construction*
"formulated to be suitable for administration to a patient upon manufacture without dilution or reconstitution"	"suitable for administration to a patient without requiring dilution"

The parties agree on much of the construction of "ready to use": that it is suitable for administration to a patient without dilution. However, Fresenius Kabi's construction, which goes no further, is too broad. It includes, for example, syringes containing the old concentrated version of Precedex™ that had been diluted by hospital personnel prior to administration. Such diluted compositions are plainly beyond the scope of the invention here. Only Hospira's construction captures that the claimed "ready to use" composition is manufactured for direct administration to patients without any dilution (or, similarly, reconstitution).

The patents' specification explains that "ready to use" compositions are "premixed compositions that are suitable for administration to a patient without dilution." (JA-3 at 3:56-59.) In turn, a "premixed composition" is a "pharmaceutical formulation that does not require reconstitution or dilution prior to administration to a patient" by anyone at any time—"in contrast to non-premixed formulations of dexmedetomidine, the premixed compositions provided herein are suitable for administration to a patient without dilution by, for example, a clinician, hospital personnel, caretaker, patient or any other individual." (JA-3 at 3:48-55.)

The key feature of the claimed "ready to use" formulation is that there is no user dilution at any time prior to administration. The specification explains that "[t]he requirement of a dilution step in the preparation of the dexmedetomidine formulation is associated with additional costs and inconvenience, as well as the risk of possible contamination or overdose due to human error." (JA-2 at 1:50-53.) The claimed "ready to use" composition eliminates this dilution step:

> The present invention is based in part on the discovery that dexmedetomidine prepared in a premixed formulation that does not require reconstitution or dilution prior to administration to a patient, remains stable and active after prolonged storage. Such premixed formulations therefore avoid the cost, inconvenience, and risk of contamination or overdose that can be associated with reconstituting or diluting a concentrated dexmedetomidine formulation prior to administration to a patient.

(JA-2 – JA-3 at 2:62-3:3; *see also* JA-2 at 1:53-57.) To eliminate the dilution step, the "ready to use" composition must be "***formulated*** as a premixed composition." (JA-2 at 1:61-67 ("The present invention relates to premixed pharmaceutical compositions of dexmedetomidine, or a pharmaceutically acceptable salt thereof, that are formulated for administration to a patient, without the need to reconstitute or dilute the composition prior to administration. Thus, the compositions of the present invention are formulated as a premixed composition comprising dexmedetomidine.").) To avoid the need for dilution, the inventors developed a composition that could be manufactured in diluted form and that would maintain long-term stability during storage. (*E.g.*, JA-1041 ("[U]nlike the claimed ready to use liquid pharmaceutical composition, which can be stored for prolonged periods of time, the diluted composition described by the Precedex™ label is prepared for use within a 24 hour period, and is not a formulation suitable for prolonged storage. Accordingly, while diluting a 100 µg/mL concentrate to a 4 µg/mL dilution produces a composition that is stable and useable for a 24 hour period after dilution, the claimed

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