## REMARKS

The present application is a divisional application of Serial No. 13/353,653.

Original claims 1-18 are canceled without prejudice and new claims 19-48 are added.

## I. SUPPORT FOR NEW CLAIMS

New claims 19-48 are supported by the original specification and claims.

New claim 19 is supported by original claims 1 and 3; page 7 lines 14-15 and lines 26-28; page 8 lines 16-18; and Experimental Example 1.

New claim 20 is supported by the paragraph bridging pages 3-4.

New claim 21 is supported by page 8 lines 6-10.

New claims 22-23 are supported by page 11 lines 1-6; and page 8 lines 19-26.

New claim 24 is supported by page 6 lines 8-10.

New claim 25 is supported by the compositions of Tables 1 and 2 and page 12 line 23. Note that sodium tetraborate is known as borax and EDTA sodium salt is known as sodium edetate.

New claim 26 is supported as noted above and further supported by Table 2 on page 17 to page 18 line 7.

New claim 27 is supported as noted above.

New claim 28 is supported as noted above and further supported by Table 2.

News claims 29-31 are supported as noted above.

New claim 32 is supported as noted above and further supported by page 12 line 14.

New claims 33-43 are supported as noted above.

New claims 44-48 are supported by Experimental Example 3 on pages 18-22 of the specification.

## II. THE SUBJECT MATTER OF NEW CLAIMS 19-48 IS PATENTABLE

Applicant respectfully submits that the subject matter of new claims 19-48 is patentable over the prior art, particularly U.S. Patent No. 5,603,929 to Desai et al. ("Desai").

As an initial matter, Applicant notes that amendments and/or arguments made in the parent applications of the present case to distinguish the prior art do not carry forward and should

not apply to the claims in this application.[1] *See, Hakim v. Cannon Avent Gp., plc*, 479 F.3d 1313 (Fed. Cir. 2007) (permitting rescission of disclaimer and recapture of disclaimed scope so long as that rescission is made clear on the record). The present claims are different and do not, for example, recite the limitation that "when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is limited to benzalkonium chloride."

Desai does not disclose the currently claimed composition, with the ingredients combined as recited in the claims. Indeed, one skilled in the art would have interpreted Desai, at a time before applicant's invention, as disclosing a narrow and specific composition that differs significantly from that currently claimed by Applicant.

Desai's objective is to provide a preservative system, the efficacy of which is not degraded or reduced in the presence of an acidic drug (such as diclofenac) that is incompatible with positively charged preservatives. (Desai, column 1, lines 27-34, and column 2, lines 10-14.) Desai stated that its objective was achieved by combining a polymeric quaternary ammonium compound (also known as "polyquat") and boric acid. (Desai, column 2, lines 18-22.) The specification of the Desai patent presented preservative efficacy data for only one formulation (Formulation A). But in addition to a polyquat and boric acid, Formulation A also contained mannitol. (Desai, Example 1, column 4, lines 15-33.) During prosecution, Desai submitted a declaration providing comparative data to show that only the formulation having polyquat-1, though it also contained boric acid and mannitol, satisfied the preservative efficacy criteria, whereas formulations having benzalkonium chloride or benzothenium bromide did not. (Desai's Declaration dated 2/26/1996, Table 2, a copy of which is attached hereto) Desai made a statement regarding the role of mannitol in his compositions, contending it did not have any significant effect on preservative efficacy. (Desai's Supplemental Declaration, dated 7/2/1996, a copy of which is attached hereto) Those skilled in the art, however, would have had a much different understanding of Desai's disclosure and the role of mannitol prior to the time of the present invention.

That Desai's formulation satisfies the preservative efficacy was not due solely to polyquat-1 and boric acid, but to the combination of polyquat-1, boric acid, and mannitol. It had

---

[1] The parent applications are Serial No. 13/353,653, filed January 19, 2012, and Serial No. 10/525,006, filed March 28, 2005, now issued as U.S. Patent No. 8,129,431.

been known even before Desai[2] that borate/polyol complexes worked as preservative systems. *See*, *e.g.*, U.S. Patent No. 5,342,620 to Chowhan, cited by the examiner of the Desai's patent. Borate/polyol complexes enhance the preservative efficacy of a weak preservative, or a preservative amount, that otherwise would not satisfy the preservative efficacy standards. (Chowhan '620, column 1, line 67 to column 2, line 7.) Reading the Desai patent with the knowledge available in the art before Applicant's invention, the skilled artisan would have recognized that the borate/polyol complex, as a whole, contributed to increase the preservative efficacy of polyquat-1—not just boric acid.

Indeed, at the time Desai filed his application for patent, it was already known that mannitol acted to enhance the preservative efficacy of a weak preservative. For example, U.S. Patent No. 5,505,953 issued to Chowhan ("Chowhan '953") provided a comparison of the preservative efficacy of formulations with and without mannitol. (Chowhan '953, column 9, line 15 to column 10, line 26.) The formulations without mannitol failed to meet the British Pharmacopeia (1988) standards. (Chowhan '953, column 9, lines 44-48, and column 10, lines 21-25.) To the best of Applicant's knowledge, the preservative efficacy acceptance criteria of British Pharmacopeia and European Pharmacopeia are similar. Therefore, Chowhan '620 and Chowhan '953 showed that, without mannitol, Desai's objective of meeting the preservative efficacy standard of both US Pharmacopeia XXII and European Pharmacopeia would not have been achieved.

Applicant has experimental results that corroborate what those skilled in the art already knew at the time of Desai and certainly before Applicant's invention: 1) that without mannitol, Desai's combination of only polyquat-1, at a concentration typically used in ophthalmic formulations, and boric acid does not satisfy preservative efficacy criteria, even for the US Pharmacopeia, and 2) that the Desai patent would have been interpreted as requiring the presence of mannitol in addition to boric acid to achieve the touted preservative efficacy.

In this regard, Applicant presents Tables 1 and 2. Table 1 provides the compositional details of six diclofenac formulations, some of which contain mannitol with polyquat-1 and boric acid, and some of which do not contain mannitol. Table 2 provides the preservative efficacy of the preservative in each formulation in Table 1.

---

[2] Desai published in February 1997, well before the present application's Japanese priority filing in January 2003.

In Table 1, DBP-1 corresponds closely to Desai's Formulations B and C. It also contains 3.5%w/v of mannitol, whereas Formulation B of Desai contains 1.6 %w/v of mannitol. The 0.005% w/v of polyquat-1 used in Desai's Formulations B and C, as well as in DBP-1, is a typical concentration for this preservative. Desai's Formulation A, on the other hand, has a much higher concentration—4% polyquat-1, a level not typically used in commercial ophthalmic products. Conducting the experiments, therefore, at 0.005% polyquat-1 more effectively shows the importance of mannitol in achieving Desai's stated purpose.

DBP-2 is the same as DBP-1, except it had a pH of 7.8 to discern any effect of pH.

DBP-3 and DBP-4 correspond to DBP-1 and DBP-2, respectively, without mannitol. The results for these formulations show the requirement of mannitol in Desai's formuation.

DBP-5 and DBP-6 correspond to DBP-1 and DBP-2, respectively, without mannitol, but with tyloxapol. Tyloxapol is not a polyol but a polyether.

**Table 1. Diclofenac/boric acid/polyol matrix**

| Ingredient | DBP-1 (%w/v) | DBP-2 (%w/v) | DBP-3 (%w/v) | DBP-4 (%w/v) | DBP-5 (%w/v) | DBP-6 (%w/v) |
|---|---|---|---|---|---|---|
| Sodium Diclofenac | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| HPMC (E4M) | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Tromethamine | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 |
| Boric Acid | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 |
| Vitamin E TPGS | 3.0 | 3.0 | 3.0 | 3.0 | 3.0 | 3.0 |
| Mannitol | 3.5 | 3.5 | --- | --- | --- | --- |
| Polyquaternium-1 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 |
| Tyloxapol | --- | --- | --- | --- | 0.02 | 0.02 |
| HCl/NaOH | pH to 7.4 | pH to 7.8 | pH to 7.4 | pH to 7.8 | pH to 7.4 | pH to 7.8 |
| Purified Water | qs to 100% | qs to 100% | qs to 100% | qs to 100% | qs to 100% | qs to 100% |

Table 2 is a collection of tables presenting the preservative efficacy testing results for each of the foregoing formulations.

**Table 2. Preservative Efficacy Testing Results**

**DBP-1: Diclofenac + Mannitol + PQ-1 pH 7.4**

| Organism | Time Intervals | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 hr | 6 hr | 24 hr | 48 hr | 7 day | 14 day | 28 day |
| *A. brasiliensis* | 0.02 | 0.06 | 2.12 | 2.99 | 3.10 | ~3.79 | ~3.42 |
| *C. Albicans* | 1.01 | 2.99 | >4.51 | >4.51 | >4.51 | >4.51 | >4.51 |
| *E. coli* | 2.65 | >4.24 | >4.24 | >4.24 | >4.24 | >4.24 | >4.24 |
| *S. aureus* | ~3.43 | >4.49 | >4.49 | >4.49 | >4.49 | >4.49 | >4.49 |
| *P. aeruginosa* | >4.64 | >4.64 | >4.64 | >4.64 | >4.64 | >4.64 | >4.64 |

**DBP-2: Diclofenac + Mannitol + PQ-1 pH 7.8**

| Organism | Time Intervals | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 hr | 6 hr | 24 hr | 48 hr | 7 day | 14 day | 28 day |
| *A. brasiliensis* | 0.05 | 0.09 | 1.35 | 2.82 | 2.28 | 2.39 | 2.59 |
| *C. Albicans* | 0.83 | 3.06 | >4.51 | >4.51 | >4.51 | >4.51 | >4.51 |
| *E. coli* | 3.06 | >4.24 | >4.24 | >4.24 | >4.24 | >4.24 | >4.24 |
| *S. aureus* | ~3.52 | >4.49 | >4.49 | >4.49 | >4.49 | >4.49 | >4.49 |
| *P. aeruginosa* | >4.64 | >4.64 | >4.64 | >4.64 | >4.64 | >4.64 | >4.64 |

**DBP-3: Diclofenac + PQ-1 pH 7.4 (No Mannitol)**

| Organism | Time Intervals | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 hr | 6 hr | 24 hr | 48 hr | 7 day | 14 day | 28 day |
| *A. brasiliensis* | 0.03 | 0.34 | 2.01 | ~4.01 | 3.05 | 2.95 | 2.61 |
| *C. Albicans* | ~3.48 | >4.51 | >4.51 | >4.51 | >4.51 | >4.51 | >4.51 |

DOCKET ALARM

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

**LAW FIRMS**
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

**FINANCIAL INSTITUTIONS**
Litigation and bankruptcy checks for companies and debtors.

**E-DISCOVERY AND LEGAL VENDORS**
Sync your system to PACER to automate legal marketing.