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HAYNES, D.S. et al., 'Intratympanic dexamethasone for sudden sensorineural hearing loss after failure of systemic therapy', Laryngoscope. 2007, Vol. 117, No. 1, pp. 3-15
LAWRASON HUGHES, A. et al., 'Dexamethasone Otoprotection in a Multidose Cisplatin Ototoxicity Mouse Model', Otolaryngology–Head and Neck Surgery. 2014, Vol. 150, No. 1, pp. 115-20

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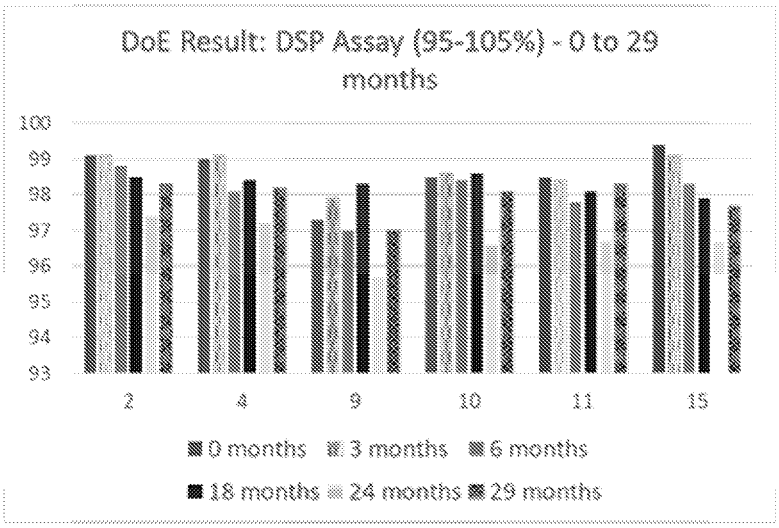
(54) Title: STABLE GLUCOCORTICOID FORMULATION

Figure 1



(57) Abstract: This invention relates to aqueous pharmaceutical formulations comprising a glucocorticoid. These have been formulated to contain high concentrations of glucocorticoid and reduced levels of preservatives.

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STABLE GLUCOCORTICOID FORMULATION

FIELD

[0001] The present invention relates to stable glucocorticoid formulations with low concentrations of preservatives. More particularly, the present invention relates to high concentration formulations of a glucocorticoid-containing aqueous pharmaceutical composition that is formulated with low levels of antioxidant acting preservatives. Such preservatives that have previously been formulated at high dose levels have been found to be associated with patient toxicity. Accordingly, the ability to achieve continued drug stability and purity in the presence of low levels of antioxidants, as disclosed herein, is highly desirable.

BACKGROUND

[0002] There are many reported disadvantages associated with the use of preservatives and antioxidants typically added to pharmaceutical compositions to maintain stability. (American Hospital Formulary Service. Volumes I and II. Washington, DC: American Society of Hospital Pharmacists, to 1984., p. 40:08). For example, the field of pediatrics is struggling with toxic excipients of liquid formulations to the extent that an entire industry is making an effort to switch to new solid formulation forms (mini-tablets, orodisperse films etc.; Thabet et al. 2018). The European Paediatric Formulation Initiative is working on the "Safety and Toxicity of Excipients for Paediatrics" (STEP) - database, which provides toxicologic information (thresholds etc.) on selected pharmaceutical excipients for pediatric use. (see http://www.eupfi.org/step-database-info/). New liquid formulations with excipients either absent from the STEP database list or without a set threshold are desperately needed.

[0003] Parabens are a class of widely used preservatives in both cosmetic and pharmaceutical products. There are reports that parabens are associated with toxic side effects – for example, the controversial status of propylparaben concerning reproductive toxicity (Oishi et al., 2002) has not yet been resolved (excipient no longer covered by the European Food Safety Authority (EFSA) entry for food additives; EFSA unable to recommend a specific acceptable daily intake (ADI)). Parabens were associated with aeroallergen sensitization (Savage et al. 2012; Spanier et al. 2014) and an increase in the potential risk of allergic disease. In particular when administered as a high-dose bolus due to compounding formulations (increased levels), parabens might become a dangerous trigger for allergies.

[0004] Benzyl alcohol is used as a bacteriostatic preservative at low concentration in a number of intravenous medications, cosmetics, and topical drugs. Benzyl alcohol's severe toxicity regarding neonates is well-recognised (Gershanik et al., 1982; Hiller et al., 1986; Benda et al., 1986; Jardine and Rogers at al., 1989). Due to its generally recognized toxicity (neural, hemolytic, mucous membrane irritant), the World Health Organisation (Joint FAO/WHO Expert Committee on Food Additives; JECFA) set an ADI treshold of 5 mg/kg.

[0005] Benzethonium chloride is used as a preservative in pharmaceutical and cosmetic products. It is an irritant and allergic sensitizer in humans (Benjamin et al. 2011, Dao et al. 2012). Very recent data suggests that it could potentially exacerbate inflammatory bowel disease and associated colon cancer (Sanidad et al. 2018).

[0006] Propylene glycol is used as a vehicle for topical, oral, and intravenous pharmaceutical preparations. It may also be used as a preservative in pharmaceutical and cosmetic products. Propylene glycol, given in amounts $\geq$ 3 g/day IV, can accumulate and cause lactic acidosis, CNS depression, coma, hypoglycemia, seizures, and hemolysis (Lim et al. 2014). Patients at risk for toxicity include infants, patients with renal insufficiency or patients with epilepsy. Therefore the Committee for Human Medicinal Products, EMA/CHMP/334655/2013 (Nov 2014) has set thresholds of 1 mg/kg (neonates up to 28 days), 50 mg/kg (29 days up to 4 years), 500 mg/kg (5 years up to 17 years and adults).

[0007] Creatinine has been used as a stabilizing excipient for high-concentration, low volume Dexamethasone Sodium Phosphate (DSP; withdrawn) formulations in the past. Intravenous administration of those formulations lead to artifactually elevated patient creatinine lab results due to analytically correct measurement of creatinine added as an excipient (Darby et al. 2012).

[0008] Sulfites are also widely used as preservative and antioxidant additives in the pharmaceutical industries. Exposure to such sulfites has been reported to induce a range of adverse clinical effects in sensitive individuals, ranging from dermatitis, urticaria, flushing, hypotension and abdominal pain to life-threatening anaphylactic and asthmatic reactions. Sulfite-inducing symptoms range from mild in some individuals, to severe in others, and in some individuals the reactions can be life threatening (See, EFSA Journal 2016;14(4):4438; https://www.efsa.europa.eu/en/efsajournal/pub/4438).

[0009] Obtaining the stability of a drug formulation without the potential toxicological side effects of preservatives and stabilizers can be difficult to achieve and it is difficult to prevent adverse and/or safety issues from occuring. More specifically, the concentration of a preservative necessary for stability of the formulation may create the potential for toxicological effects. Using lower concentrations of the preservative may help to reduce the potential for such toxicological side effects, but the lower concentrations of the preservatives may also be inadequate to achieve the desired assay level. That is, using lower concentrations of the preservative may help to reduce the potential for such toxicological side effects, but the lower concentrations of the preservatives may also be inadequate to maintain required levels of chemical and physical stability of the formulation over time. Stability of the formulation over time may be determined, for example, by assaying quantitative chemical attributes of the formulation such as levels of the active pharmaceutical ingredient (API) or its degradation products.

[0010] As stated above, pharmaceutical compositions typically require the addition of preservatives, stabilizers, and antioxidant additives such as sodium sulfite to maintain the stability of the composition. Examples of such pharmaceutical compositions include solutions and suspensions that are injected into the bodies of humans or other mammals. For such parenteral products, where inert gases as well as nitrogen are used as the interior gas within the vials of injectables, manufacturers strive to reach a 100% level of saturation of a chosen gas within the vial headspace in order to restrict the amount of oxygen which can contribute to oxidative degradation of the API. However, due to manufacturing limitations during good manufacturing practice (GMP) manufacture and filling, it is possible for trace amounts of oxygen to be introduced inadvertently, reducing the product's shelf-life and stability when compared to its registration label.

[0011] Furthermore, since it is known that no containers are perfectly gas tight (e.g. tested for stoppered vials with lyophilized product: ~1.3% atm oxygen permeation per year; Lighthouse Instruments webinar "Determining & Controlling Oxygen Levels in Sensitive Formulations" - https://www2.lighthouseinstruments.com/l/302881/2018-02-26/2nytk), oxygen permeates into the vials over time. Permeation occurs either through the rubber stopper material of the vial or through microchannels between the rubber stopper and the vial neck interphase.

[0012] Therefore, when a new formulation is planned, a threshold of headspace oxygen needs to be considered. Knowing the impact of excess oxygen allows the manufacturer to calculate the impact on stability of the drug product and potentially reduce the quantity of excipient utilized in that formulation. Formulations with increasing amounts of oxygen content in percent can be manufactured for Design of Experiment (DoE) studies to simulate a worst-case scenario. The formulations with varying levels of headspace oxygen are then set on stability and eventually an assay and shelf-life is determined for increasing levels of oxygen. That is, the formulations with varying levels of headspace oxygen are then tested for stability and an assay of quantitative chemical attributes (e.g. API amount, presence of degradation products, pH, etc.) and shelf-life is determined for increasing levels of oxygen.

[0013] Means for determining headspace oxygen levels in a given headspace volume are well known to those skilled in the art. For example, headspace oxygen levels may be measured by conventional destructive techniques, such as electrochemical methods or gas chromatography, or by non-destructive methods such as laser-based Frequency Modulation Spectroscopy (Pharmaceutical Technology, July 2002; Lighthouse Instruments Application Note 102).

[0014] Such compositions and formulations once packaged can therefore carry trace amounts of oxygen from the manufacturing process, thereby decreasing the stability of the composition or formulation. Moreover, aside from degrading oxidative processes, hydrolyzation contributes to degradation of the API and reduces the assay as well as increases the accumulation of unwanted impurities above a safe threshold.

[0015] Accordingly, it is necessary to employ a means for preventing such degradation from occurring and the means employed may be the addition of an antioxidant, stabilizer, and/or antimicrobial chemical agent (herein referred to as "preservative") that maintains the assay of the composition.

[0016] Decadron™ 24 mg/ml, manufactured by Merck (withdrawn) had a headspace volume to API ratio of 0.0075 and a "(Sulfite : API) x headspace" value of 0.03750, with antioxidants (preservatives) present at 1 mg/ml sodium bisulfite, 1.5 mg/ml methylparaben, 0.2 mg/ml propylparaben, 8 mg/ml creatinine. DBL™ Dexamethasone Sodium Phosphate 24 mg/ml, manufactured by Hospira (withdrawn) had a headspace volume to API ratio of 0.0075, with antioxidants (preservatives) present at 8 mg/ml creatinine and 0.5 mg/ml disodium edetate.

Solcort™ 24 mg/ml manufactured by Fuji Pharma (Japan) has a headspace volume to API ratio of 0.0075, with antioxidants (preservatives) present at 0.5 mg/5 ml Benzethonium chloride.

[0017] Dexamethasone 10 mg/ml, manufactured by Hameln Pharmaceuticals has a headspace volume to API ratio of 0.0075 with propylene glycol and disodium edetate as antioxidants (preservatives). Dexamethasone Sodium Phosphate 10 mg/ml, distributed by Physicians Total Care, Inc. has a headspace volume to API ratio of 0.01920 and a "(Sulfite : API) x headspace" - value of 0.19200 and antioxidants (preservatives) of 1 mg/ml sodium metabisulfite and 10 mg/ml benzyl alcohol. Dexamethasone Sodium Phosphate 10 mg/ml, manufactured by West-Ward Pharmaceuticals Corp. has a headspace volume to API ratio of 0.02 and a "(Sulfite : API) x headspace" - value of 0.03, with antioxidants (preservatives) present at 1.5 mg/ml sodium sulfite 10.42 mg/ml benzyl alcohol. Dexamethasone Sodium Phosphate 10 mg/ml, manufactured by Mylan has a headspace volume to API ratio of 0.02 and antioxidants (preservatives) of 1.5 mg/ml methylparaben, 0.2 mg/ml propylparaben, 0.11 mg/ml disodium edetate (0.11 mg in 1 mL). Dexamethasone Sodium Phosphate (preservative free) 10 mg/ml (only 1 ml total volume), manufactured by Fresenius has a headspace volume to API ratio of 0.02. Dexamethasone Sodium Phosphate (preserved) 10 mg/ml (10 ml total volume), manufactured by Fresenius has a headspace volume to API ratio of 0.0404 and antioxidants (preservatives) present at 10 mg/ml benzyl alcohol.

[0018] Dexamethasone Sodium Phosphate 4 mg/ml, manufactured by West-Ward Pharmaceuticals Corp. has a headspace volume to API ratio of 0.0375 and a "(Sulfite : API) x headspace" - ratio of 0.1875, with antioxidants (preservatives) present at 1 mg/ml sodium sulfite anhydrous, 10.42 mg/ml benzyl alcohol. Dexamethasone 4 mg/ml (2 ml total volume), manufactured by Hospira has a headspace volume to API ratio of 0.05 and a "(Sulfite : API) x headspace" - ratio of 0.007 with antioxidants (preservatives) present at 0.5 mg/ml disodium edetate, 0.07 mg/ml sodium sulphite anhydrous.

[0019] Dexaject SP 3.66 mg/ml, manufactured by Henry Schein Animal Health has a headspace volume to API ratio of 0.04918 and a "(Sulfite : API) x headspace" - ratio of 9.836 with antioxidants (preservatives) present at 2 mg/ml sodium bisulfite, 1.5% benzyl alcohol.

[0020] These and other dexamethasone-containing formulations are described in Supplementary Tables A-F.

[0021] Thus, there is a need for a means to maintain the stability of the pharmaceutical environment so that very low concentrations of preservatives can be utilized without reducing the shelf-life of the product to the extent where the product would no longer be safely administered.

[0022] A need exists for a means to maintain the stability of aqueous pharmaceutical formulations comprising a glucocorticoid with low concentrations of preservatives. Aqueous pharmaceutical formulations comprising a glucocorticoid and low or no amounts of preservative without reduced stability or shelf-life are desired.

SUMMARY

[0023] The following brief summary is not intended to include all features and aspects of the present invention, nor does it imply that the invention must include all features and aspects discussed in this summary.

[0024] The present disclosure is directed to high concentration glucocorticoid-containing pharmaceutical compositions comprising reduced levels of antioxidant-acting preservatives. More particularly, the present disclosure is directed to aqueous pharmaceutical formulations comprising a glucocorticoid. The pharmaceutical formulations disclosed herein comprise reduced levels of preservative and / or chelating agent as compared to known glucocorticoid-containing formulations.

[0025] The present disclosure is based on the finding that use of a defined headspace volume to API ratio during the filling of the formulation into vials results in a maintained stability of the compositions close to the state directly after manufacture in the presence of reduced levels of antioxidant preservatives.

[0026] That is, the present disclosure is based on the finding that use of a defined headspace volume (ml) to glucocorticoid (mg) ratio during packaging of the glucocorticoid containing formulation into containers (e.g. vials) results in stability of the formulation being maintained close to its state directly after manufacture. Surprisingly, this effect is observed even when the formulation comprises reduced or no amounts of preservative (e.g. antioxidants). The defined

headspace volume (ml) to glucocorticoid (mg) ratio disclosed herein is lower than that used in known glucocorticoid formulations (see Example 1, Table 1).

[0027] Without being bound by theory, it is believed that use of a defined headspace volume (ml) to glucocorticoid (mg) ratio as disclosed herein (and which is lower than that used in known glucocorticoid formulations) results in fewer oxygen molecules being present per given molecule of glucocorticoid. Accordingly, a given amount of glucocorticoid molecules is presented with fewer oxygen molecules resulting in less oxidative degradation (and accumulation of impurities over time).

[0028] More specifically, the present invention is based on a finding that reduced headspace volume to API ratio, beyond typical manufacturing (see Table 1), allows sulfite preservatives to be 35 ppm or lower as well as chelators (Disodium Edetate) to be 500 ppm or lower (Example 2) to achieve at least a minimum of 24 months shelf-life at between 2^0C to 30^OC (Table 4, Fig. 1 – 26).

[0029] That is, the present authors have demonstrated that use of such a reduced headspace volume (ml) to glucocorticoid (mg) ratio allows sulfite preservatives to be present at 0.035 mg/ml (35 ppm) or less, and chelating agent (Disodium Edetate) to be present at 0.5 mg/ml (500 ppm) or less in a formulation with up to 48 months shelf-life when stored at 25°C/ 60% RH (see Example 2).

[0030] Moreover, the present invention is additionally based on the finding that Dexamethasone Sodium Phosphate (DSP) in higher concentration in a solution becomes increasingly self-protective as an API (concentration dependence not known in the industry) against degrading processes like hydrolyzation and oxidization, enabling the above ranges of 0-35 ppm for sulfite preservatives and 0-500 ppm for chelators (Disodium Edetate).

[0031] That is, the present disclosure is also based on the unexpected finding that the glucocorticoid Dexamethasone Sodium Phosphate (DSP), when present in high concentrations in an aqueous formulation, is increasingly self-protective against degradative processes like hydrolyzation and oxidization. This concentration-dependent self-protection, which has not previously been reported, also contributes to stability of the disclosed aqueous formulations

[0032] These unexpected findings of the present authors allow for the manufacture of aqueous pharmaceutical formulations comprising a glucocorticoid and low or no amounts of preservative and / or chelating agent, which formulations have shelf-lives which are comparable to, or longer than, those of known preservative-containing glucocorticoid formulations. That is, the compositions and formulations of the invention allow for long-term storage of glucocorticoid solutions which contain low or no amounts of preservative and / or chelating agent.

[0033] Accordingly, in a first aspect, the invention provides a pharmaceutical composition comprising (i) a glucocorticoid, packaged with a headspace (volume; [ml]) to glucocorticoid (weight [mg]) ratio of 0 – 0.00588, and (ii) a preservative in a concentration of less than 70 ppm.

[0034] The pharmaceutical compositions of the present invention offer several advantages over existing formulations. Given that antioxidant preservatives have been found to be associated with patient sensitivity and toxicity, pharmaceutical compositions comprising lower levels of such preservatives, while retaining stability of the composition, is highly desirable. In a specific embodiment of this invention, the antioxidant is Sodium Sulfite (Anhydrous), an excipient absent from the STEP – database, which is monitoring toxic excipients for use in pediatric populations (Thabet et al. 2018; Nellis et al. 2015; Turner et al. 2014). In a specific embodiment of the invention, AVM0703 refers to the initial target formulation of the DoE study (see Formulations 2, 4, 6, 8, 12 in Tables 4-7).

[0035] In a second aspect, the invention provides a method for producing a pharmaceutical composition having a low concentration of preservative, based on packing of said pharmaceutical composition with a headspace (volume; [ml]) to glucocorticoid (weight [mg]) ratio of 0 – 0.00588.

[0036] As outlined above, the present disclosure also relates to methods for production of high concentration glucocorticoid containing pharmaceutical compositions comprising reduced levels of antioxidant preservatives. Such methods comprise the step of mixing components of the composition and packaging said composition in an environment wherein the headspace volume to API ratio as well as the antioxidant to total API ratio is decreased.

[0037] In a third aspect, the invention provides a method of treating a host in need of glucocorticoid treatment, comprising administering a pharmaceutical compositon of the invention. That is, the present disclosure is further directed to use of the pharmaceutical compositions disclosed herein for treatment of patients in need of glucocorticoid drugs. Such methods of treating a host include administration of the compositions to patients in need of anti-inflammatory, immunosuppression, lymphoablation, germinal center elimination, IL-2 IL-7 IL-12 and/or IL-15 elevation, mesenchymal stem cell elevation, G-CSF increase, neutrophil increase, tumor/cancer killing or lymphodepletion (preconditioning) before cell-based therapy, FGF-18 elevation, cartilage production, hematopoietic stem cell elevation and/or neutrophil production, or improvement in Performance Status among patients with diseases that include but are not limited to cancer and autoimmune diseases, for example.

[0038] In a fourth aspect, the invention provides an aqueous pharmaceutical formulation comprising dexamethasone and a preservative, wherein the formulation is packaged in a container with a headspace volume (ml) to dexamethasone content (mg) ratio of 0.007 or less, and wherein the concentration of preservative is or is less than about 0.1 mg/ml. The present inventors have found that use of a defined headspace volume (ml) to glucocorticoid (mg) ratio during packaging of the glucocorticoid containing formulation into containers (e.g. vials) results in stability of the formulation being maintained close to its state directly after manufacture. Surprisingly, this effect is observed even when the formulation comprises reduced or no amounts of preservative (e.g. antioxidants).

[0039] In some embodiments, the dexamethasone is dexamethasone sodium phosphate. In some embodiments, the concentration of dexamethasone phosphate in the formulation is at least 24 mg/ml. In some embodiments, the headspace volume (ml) to dexamethasone content (mg) ratio is 0.00588 or less. In some embodiments, the headspace volume comprises less than about 10 % oxygen, more preferably less than about 5 % oxygen.

[0040] In some embodiments, the concentration of preservative is or is less than about 0.035 mg/ml. In some embodiments, the preservative is a sulfite, a paraben, benzyl alcohol, benzethonium chloride, propylene glycol, and / or creatinine. In some embodiments, the sulfite is sodium sulfite (anhydrous), sodium bisulfite, and / or sodium metabisulfite. In some particularly preferred embodiments, the formulation does not comprise a preservative. The present inventors have demonstrated that use of the defined headspace volume (ml) to

glucocorticoid (mg) ratios of the present invention allows the formulations of the invention to remain stable up to 29 months (and projected up to 48 months) after manufacture, even with low or no amounts of preservative.

[0041] In some embodiments the formulation comprises one or more chelating agent. In some embodiments, the concentration of chelating agent is or is less than about 0.50 mg/ml. In some embodiments, the chelating agent is disodium edetate (disodium EDTA). In some particularly preferred embodiments, the formulation does not comprise a chelating agent. The present inventors have demonstrated that use of the defined headspace volume (ml) to glucocorticoid (mg) ratios of the present invention allows the formulations of the invention to remain stable without use of a chelating agent.

[0042] In some embodiments, the dexamethasone is selected from the group consisting of dexamethasone base, dexamethasone sodium phosphate and dexamethasone acetate. In some preferred embodiments, the dexamethasone is dexamethasone sodium phosphate.

[0043] In some embodiments, the shelf-life of the formulation is at least about 18, 24, 36, or 48 months when stored between 2°C to 40°C. In some embodiments, the formulation remains stable when stored between 2°C to 40°C for at least about 18, 24, 36, or 48 months.

[0044] In some embodiments, the amount of glucocorticoid in the formulation is maintained between ± 5.0 % as compared to the date of manufacture when the formulation is stored between 2°C to 40°C for at least about 18, 24, 36, or 48 months. In some embodiments, the formulation exhibits less than ± 0.5 change in pH when stored between 2°C to 40°C for at least about 18, 24, 36, or 48 months.

[0045] In some embodiments, the formulation exhibits less than about 0.50 % accumulation of impurity A when stored between 2°C to 40°C for at least about 18, 24, 36, or 48 months. In some embodiments, the formulation exhibits less than about 0.50 % accumulation of impurity B when stored between 2°C to 40°C for at least about 18, 24, 36, or 48 months. In some embodiments the formulation exhibits less than about 0.50 % accumulation of impurity G when stored between 2°C to 40°C for at least about 18, 24, 36, or 48 months. In some embodiments, the formulation exhibits less than about 0.20 % accumulation of unspecified impurities when stored between 2°C to 40°C for at least about 18, 24, 36, or 48 months. In

some embodiments, the formulation exhibits less than about 3.0 % accumulation of total impurities when stored between 2°C to 40°C for at least about 18, 24, 36, or 48 months.

[0046] In a fifth aspect, the invention provides an aqueous pharmaceutical formulation as defined herein, for use in a method of treatment.

[0047] In a sixth aspect, the invention provides use of an aqueous pharmaceutical formulation as defined herein for the preparation of a medicament for use in a method of treatment.

[0048] In a seventh aspect, the invention provides a method of treatment comprising administering to a subject in need thereof, a therapeutically effective amount of an aqueous pharmaceutical formulation as defined herein.

[0049] In an eighth aspect, the invention provides a method for stabilising an aqueous pharmaceutical formulation comprising dexamethasone and a preservative, the method comprising packaging an aqueous pharmaceutical formulation as defined herein into a container with a headspace volume (ml) to dexamethasone content (mg) ratio of 0.007 or less.

[0050] The invention includes the combination of the aspects and preferred features described except where such a combination is clearly impermissible or expressly avoided.

BRIEF DESCRIPTION OF TABLES

[0051] TABLE 1 demonstrates that AVM0703 is below the values typically found in manufactured Dexamethasone Sodium Phosphate formulations in the industry concerning headspace volume [ml] to total API (Dexamethasone Phosphate equivalent) [mg] ratio, total Sulfite [mg] to total API (Dexamethasone Phosphate equivalent) [mg] ratio as well one of the lowest "(Sulfite/API) x Headspace Volume" value. Moreover, the comparison shows estimated/measured headspace volumes, API concentrations and contents, sulfite concentrations and contents as well as their calculated ratios of selected (commercially available) Dexamethasone Sodium Phosphate solutions (vials or ampouls) in the market compared to AVM0703.

[0052] TABLE 2 demonstrates the composition of the Target Point (Center Point) Formulation of the Design of Experiment in mg/ml.

[0053] TABLE 3 demonstrates the composition of the Target Point Formulation of the Design of Experiment in weight percent.

[0054] TABLE 4 demonstrates the composition of 10 of the 16 formulations that were monitored for long-term storage (25°C/60% RH). These formulations were part of the first Design of Experiment study.

[0055] TABLE 5 demonstrates six formulations with varying levels of Sodium Sulfite (Anhydrous) and Headspace Oxygen which were tested for maintaining the assay at 18 months (25°C/ 60%RH). Aside from F15 (atmospheric Oxygen level of 20.9%), all 5 other formulations (F2, 4, 9, 10 and 11) were within the required API assay or impurity thresholds. Those six were selected from 16 formulations that were manufactured for the DoE study to assess those 2 factors: 14 formulations (F1 – F13) to assess Sodium Sulfite (Anhydrous) in a range of 0 to 0.07 mg/mL and Headspace Oxygen in a range of 0 to 10%, while 2 additional formulations (F15, F16) were manufactured to assess stability at atmospheric Oxygen (20.9%) using 0.035 or 0.07 mg/ml Sodium Sulfite (Anhydrous), respectively.

[0056] TABLE 6 demonstrates nine formulations with varying levels of Sodium Sulfite (Anhydrous) and Headspace Oxygen which were tested for stability at 24 months. Aside from F15 (atmospheric Oxygen level of 20.9%), all other 8 formulations (F2, 4, 6, 8, 9, 10, 11 and 12) were within the required API assay or impurity thresholds. Those nine were selected from 15 formulations that were manufactured for the DoE study to assess those 2 factors: 13 formulations (F1 – F13) to assess Sodium Sulfite (Anhydrous) in a range of 0 to 0.07 mg/mL and Headspace Oxygen in a range of 0 to 10%, while 2 additional formulations (F15, F16) were manufactured to assess stability at atmospheric Oxygen (20.9%) using 0.035 or 0.07 mg/ml Sodium Sulfite (Anhydrous), respectively.

[0057] TABLE 7 demonstrates nine formulations with varying levels of Sodium Sulfite (Anhydrous) and Headspace Oxygen which were tested for stability at 29 months. Aside from F15 (atmospheric Oxygen level of 20.9%), all other 8 formulations (F2, 4, 6, 8, 9, 10, 11 and 12) were within the required API assay or impurity thresholds. Those nine were selected from 15 formulations that were manufactured for the DoE study to assess those 2 factors: 13 formulations (F1 – F13) to assess Sodium Sulfite (Anhydrous) in a range of 0 to 0.07 mg/mL

and Headspace Oxygen in a range of 0 to 10%, while 2 additional formulations (F15, F16) were manufactured to assess stability at atmospheric Oxygen (20.9%) using 0.035 or 0.07 mg/ml Sodium Sulfite (Anhydrous), respectively.

[0058] TABLE 8 demonstrates the composition of ten formulations used in a design of experiment series (up to 6 months at 40°C/75%RH) to assess the stability of the formulation without the presence of either sodium sulfite or EDTA at increasing levels of headspace oxygen (= HO: 0%, 5%, 10% and 15%): Ten formulations with the specifications shown in the table were manufactured (GLP grade) and tested for stability. 26.23 mg/ml DSP equals 24 mg/ml Dexamethasone Phosphate.

[0059] TABLE 9 demonstrates 10 additonally manufactured formulations for an extended DoE study which were conducted to assess the shelf-life of the formulation in the absence of Sodium Sulfite (Anhydrous) and/or Disodium Edetate at different levels of headspace oxygen (0, 5, 10, 15%). Storage conditions are 40°C/75% RH (inverted vial position) with sampling carried out at 0, 1, 3 and 6 months.

[0060] Table 10 demonstrates four additionally manufactured formulations with 2 varying levels of DSP (10 and 30 mg/ml) for an extended DoE study which was conducted to assess the shelf-life of the formulation with increasing DSP concentration in the presence or absence of Disodium Edetate (0.5 mg/ml). All four formulations contained 5% headspace oxygen (95% nitrogen) and lacked sulfite. Storage conditions are 40°C/75% RH (inverted vial position) with sampling carried out at 0, 1, 3 and 6 months.

[0061] Table 11 demonstrates two additionally manufactured formulations with 45 mg/ml DSP for an extended DoE study which was conducted to assess the shelf-life of the formulation with increasing DSP concentration in the presence or absence of Disodium Edetate (0.5 mg/ml). Both formulations contained 5% headspace oxygen (95% nitrogen) and lacked sulfite. Storage conditions are 40°C/75% RH (inverted vial position) with sampling carried out at 0, 1, 3 and 6 months.

[0062] Table 12 demonstrates the results of the additional design of experiment for increasing concentrations of Dexamethasone Sodium Phosphate (DSP). The six formulations (shown in Tables 10 and 11) with 3 varying levels of DSP (10, 30 and 45 mg/ml, equivalent to 9.15,

27.45 and 41.17 Dexamethsone Phosphate (DP)) with or without 0.5 mg/ml EDTA, respectively, were manufactured and put on stability (50 ml amber vial; 0, 1, 3, 6 months at 40°C/75%RH). All 6 formulations contained 5% headspace oxygen (95% nitrogen) and lacked sulfite. The results demonstrates that the formulations with an increasing DSP concentration form less total impurities over time.

* * *

[0063] SUPPLEMENTARY TABLE A demonstrates the excipient profile, strength and vial volumes of commercially available Dexamethasone Sodium Phosphate injectables for human use in the U.S.

[0064] SUPPLEMENTARY TABLE B demonstrates examples of Dexamethasone Sodium Phosphate formulations including their excipient profile (U.S. market).

[0065] SUPPLEMENTARY TABLE C demonstrates examples of Dexamethasone Sodium Phosphate formulations including their excipient profile (U.S. veterinary market).

[0066] SUPPLEMENTARY TABLE D demonstrates examples of high-dose Dexamethasone Sodium Phosphate formulations (injectables) including their excipient profile (international market).

[0067] SUPPLEMENTARY TABLE E demonstrates examples of previous patents disclosing Dexamethasone formulations with a much higher sulfite content.

[0068] SUPPLEMENTARY TABLE F demonstrates examples of Dexamethasone formulations including their shelf-life as disclosed by the manufacturers.

BRIEF DESCRIPTION OF THE DRAWINGS

[0069] Embodiments and experiments illustrating the principles of the invention will now be discussed with reference to the accompanying figures in which:

[0070] FIG. 1 demonstrates six formulations with varying levels of Sodium Sulfite (Anhydrous) and Headspace Oxygen which were tested for maintaining the assay at 25°C/ 60%RH (29 months). Formulation 2 and 4 (F2, 4) are target point formulations with 0.035

mg/ml Sodium Sulfite (Anhydrous) and 5% Headspace oxygen (95% nitrogen). The result demonstrates that the formulations are within a range of 95-105% DSP content for the tested values of Sodium Sulfite (Anhydrous) of 0 (F10), 0.035 (F2, 4, 11, 15) and 0.07 mg/ml (F9) at 5% (F2, 4, 9, 10), 10% (F11) and 20.90% (F15) headspace Oxygen, not dropping below 95% for any formulation tested.

[0071] FIG. 2 demonstrates that all the tested formulations are within a range of initially NMT (not more than) 0.5% for free Dexamethasone (later change to 1%; Imp A) with the exception of formulation 15 (atmospheric headspace oxygen). Tested values of Sodium Sulfite (Anhydrous) were 0 (F10), 0.035 (F2, 4, 11, 15) and 0.07 mg/ml (F9) at 5% (F2, 4, 9, 10), 10% (F11) and 20.90% (F15) headspace Oxygen. Free Dexamethasone accumulates due to acid hydrolysis from DSP (25°C/ 60%RH; 29 months).

[0072] FIG. 3 demonstrates that all the tested formulations are within a range of NMT (not more than) 0.2% for not yet identified impurities. Tested values of Sodium Sulfite (Anhydrous) were 0 (F10), 0.035 (F2, 4, 11, 15) and 0.07 mg/ml (F9) at 5% (F2, 4, 9, 10), 10% (F11) and 20.90% (F15) headspace Oxygen. Only formulation F15 (at atmospheric oxygen level) was above the threshold for the time point of 18 months and later (25°C/ 60%RH; 29 months).

[0073] FIG. 4 demonstrates that all the tested formulations are within a range of NMT (not more than) 3% for Total Impurities (consistent with USP). Tested values of Sodium Sulfite (Anhydrous) were 0 (F10), 0.035 (F2, 4, 11, 15) and 0.07 mg/ml (F9) at 5% (F2, 4, 9, 10), 10% (F11) and 20.90% (F15) headspace Oxygen (25°C/ 60%RH; 29 months).

[0074] FIG. 5 demonstrates that the target point formulations 2 and 4 (F2, F4: 0.035 mg/ml Sodium Sulfite Anhydrous, 5.4% Oxygen headspace) are expected to have an assay above 95% for the Dexamethasone Sodium Phosphate content for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0075] FIG. 6 demonstrates that formulation 9 (F9: 0.07 mg/ml Sodium Sulfite Anhydrous, 5.1% Oxygen headspace) is expected to have an assay above 95% for the Dexamethasone Sodium Phosphate content for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0076] FIG. 7 demonstrates that formulation 10 (F10: 0 mg/ml Sodium Sulfite Anhydrous, 5.1% Oxygen headspace) is expected to have an assay above 95% for the Dexamethasone Sodium Phosphate content for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0077] FIG. 8 demonstrates that formulation 11 (F11: 0.035 mg/ml Sodium Sulfite Anhydrous, 10.4% Oxygen headspace.) is expected to have an assay above 95% for the Dexamethasone Sodium Phosphate content for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0078] FIG. 9 demonstrates that formulation 15 (F15: 0.035 mg/ml Sodium Sulfite Anhydrous, 20.9% Oxygen headspace) is expected to have an assay above 95% for the Dexamethasone Sodium Phosphate content for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0079] FIG. 10 demonstrates that formulations 2 and 4 (F2, F4: 0.035 mg/ml Sodium Sulfite Anhydrous, 5.4% Oxygen headspace) are expected to below 0.5% for Impurity A for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0080] FIG. 11 demonstrates that formulation 9 (F9: 0.07 mg/ml Sodium Sulfite Anhydrous, 5.1% Oxygen headspace) is expected to be below 0.5% for Impurity A for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0081] FIG. 12 demonstrates that formulation 10 (F10: 0 mg/ml Sodium Sulfite Anhydrous, 5.1% Oxygen headspace.) is expected to be below 0.5% for Impurity A for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0082] FIG. 13 demonstrates that formulation 11 (F11: 0.035 mg/ml Sodium Sulfite Anhydrous, 10.4% Oxygen headspace) is expected to be below 0.5% for Impurity A for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0083] FIG. 14 demonstrates that formulation 15 (F15: 0.035 mg/ml Sodium Sulfite Anhydrous, 20.9% Oxygen headspace; atmospheric) crossed 0.5% for Impurity A at 24

months. The projection shows impurity A is expected to be below 1% for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0084] FIG. 15 demonstrates that formulation 2 (F2: 0.035 mg/ml Sodium Sulfite Anhydrous, 5.4% headspace oxygen) reached 0.2% for the Unspecified Impurity at 29 months, but is expected to be below 0.5% for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH)..

[0085] FIG. 16 demonstrates that formulation 4 (F4: 0.035 mg/ml Sodium Sulfite Anhydrous, 5.4% headspace oxygen.) reached 0.2% at 29 months, but is expected to be below 0.5% for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0086] FIG. 17 demonstrates that formulation 9 (F9: 0.07 mg/ml Sodium Sulfite Anhydrous, 5.1% Oxygen headspace.) is expected to cross 0.2% at about 32 months, but to be below 0.5% for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0087] FIG. 18 demonstrates that formulation 10 (F10: 0 mg/ml Sodium Sulfite Anhydrous, 5.1% Oxygen headspace.) is expected to cross 0.2% at about 32 months, but to be below 0.5% for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0088] FIG. 19 demonstrates that formulation 11 (F11: 0.035 mg/ml Sodium Sulfite Anhydrous, 10.4% Oxygen headspace.) is expected to cross 0.2% at about 31 months, but to be below 0.5% for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0089] FIG. 20 demonstrates that formulation 15 (F15: 0.035 mg/ml Sodium Sulfite Anhydrous, 20.9% Oxygen headspace; atmospheric) crossed 0.2% at 10 months, and is expected to cross 0.5% at 30 months (6 measured data points; up to 29 months, 25°C/ 60%RH).

[0090] FIG. 21 demonstrates that formulation 2 (F2: 0.035 mg/ml Sodium Sulfite Anhydrous, 5.4% Oxygen headspace.) is expected to be below 3% for Total Impurities for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0091] FIG. 22 demonstrates that formulation 4 (F4: 0.035 mg/ml Sodium Sulfite Anhydrous, 5.4% Oxygen headspace.) is expected to be below 3% for Total Impurities for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0092] FIG. 23 demonstrates that formulation 9 (F9: 0.07 mg/ml Sodium Sulfite Anhydrous, 5.1% Oxygen headspace.) is expected to be below 3% for Total Impurities for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0093] FIG. 24 demonstrates that formulation 10 (F10: 0 mg/ml Sodium Sulfite Anhydrous, 5.1% Oxygen headspace.) is expected to be below 3% for Total Impurities for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0094] FIG. 25 demonstrates that formulation 11 (F11: 0.035 mg/ml Sodium Sulfite Anhydrous, 10.4% headspace oxygen) is expected to be below 3% for Total Impurities for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0095] FIG. 26 demonstrates that formulation 15 (F15: 0.035 mg/ml Sodium Sulfite Anhydrous, 20.9% Oxygen headspace; atmospheric) is expected to be below 3% for Total Impurities for 48 months (projection with 6 measured data points; up to 29 months, 25°C/ 60%RH).

[0096] FIG. 27 demonstrates the identity and structure of known impurities (Impurity A, B, C, D, E, F, G) derived from Dexamethasone Sodium Phosphate (Dexamethasone sodium phosphate (DSP; 9-fluoro-11b,17,21-trihydroxy-16a-methylpregna-1,4-diene-3,20-dione 21-(dihydrogen phosphate) Disodium Salt) solutions during storage. Impurity A: (9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-3,20-dione (dexamethasone); Impurity B: (9-fluoro-11β,17-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-21-yl dihydrogen phosphate (betamethasone phosphate); Impurity C, D, E,F: for each impurity, one or more diastereoisomer(s) of (9-fluoro-11β,17a-dihydroxy-16-methyl-3,17-dioxo-*D*-homo-androsta-1,4-dien-17a-yl)methyl dihydrogen phosphate (undefined stereochemistry at C-16 and C-17a), or (9-fluoro-11β,17-dihydroxy-16α-methyl-3,17a-dioxo-*D*-homo-androsta-1,4-dien-17-yl)methyl dihydrogen phosphate (undefined stereochemistry at C-17); Impurity G: 9-fluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid. Equivalent USP impurity names are outlined.

[0097] FIG. 28 demonstrates ten formulations were tested for DSP assay (up to 6 months at 40°C/75%RH; 26.23 mg/ml DSP = 24 mg/ml DP) to assess the stability of the formulation without the presence of either sodium sulfite or EDTA at increasing levels of headspace oxygen (= HO: 0%, 5%, 10% and 15%): All ten formulations contained 26.23 mg/ml DSP, which is equivalent to 24 mg/ml Dexamethasone Phosphate (DP). While all ten formulations passed the description at 3 months, only the following formulations passed the description as a clear solution at the 6 months stability time point: (batch#-formulation#) 2-1 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 0% headspace oxygen), 2-2 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 5% headspace oxygen) and 3-1 (0.035 mg/ml sodium sulfite, 0.5 mg/ml EDTA, 0% headspace oxygen). All others showed precipitation at 6 months. The result shows that formulation 2-1 shows the least degradation of all formulations at the 6 months time point while still passing description (no precipitation).

[0098] FIG. 29 demonstrates the additional design of experiment result for impurity A (up to 6 months at 40°C/75%RH; 26.23 mg/ml DSP = 24 mg/ml DP) for the formulations without the presence of either sodium sulfite and/or EDTA at increasing levels of headspace oxygen (= HO: 0%, 5%, 10% and 15%): While all ten formulations passed the description at 3 months, only the following formulations passed the description as a clear solution at the 6 months stability time point: (batch#-formulation#) 2-1 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 0% headspace oxygen), 2-2 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 5% headspace oxygen) and 3-1 (0.035 mg/ml sodium sulfite, 0.5 mg/ml EDTA, 0% headspace oxygen). All others showed precipitation at 6 months. The result shows that formulation 2-1 showed the lowest accumulation of impurity A (Dexamethasone) of all formulations at the 6 months time point.

[0099] FIG. 30 demonstrates the additional design of experiment result for impurity B (up to 6 months at 40°C/75%RH; 26.23 mg/ml DSP = 24 mg/ml DP) for the formulations without the presence of either sodium sulfite and/or EDTA at increasing levels of headspace oxygen (= HO: 0%, 5%, 10% and 15%): While all ten formulations passed the description at 3 months, only the following formulations passed the description as a clear solution at the 6 months stability time point: (batch#-formulation#) 2-1 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 0% headspace oxygen), 2-2 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 5%

headspace oxygen) and 3-1 (0.035 mg/ml sodium sulfite, 0.5 mg/ml EDTA, 0% headspace oxygen). Impurity B was not increasing for any of the formulations.

[0100] FIG. 31 demonstrates the additional design of experiment result for impurity C (up to 6 months at 40°C/75%RH; 26.23 mg/ml DSP = 24 mg/ml DP) for the formulations without the presence of either sodium sulfite and/or EDTA at increasing levels of headspace oxygen (= HO: 0%, 5%, 10% and 15%): While all ten formulations passed the description at 3 months, only the following formulations passed the description as a clear solution at the 6 months stability time point: (batch#-formulation#) 2-1 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 0% headspace oxygen), 2-2 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 5% headspace oxygen) and 3-1 (0.035 mg/ml sodium sulfite, 0.5 mg/ml EDTA, 0% headspace oxygen). All others showed precipitation at 6 months. The result shows that the formulations with the highest headspace oxygen value showed the lowest accumulation of impurity C of all formulations at the 6 months time point.

[0101] FIG. 32 demonstrates the additional design of experiment result for impurity D (up to 6 months at 40°C/75%RH; 26.23 mg/ml DSP = 24 mg/ml DP) for the formulations without the presence of either sodium sulfite and/or EDTA at increasing levels of headspace oxygen (= HO: 0%, 5%, 10% and 15%): While all ten formulations passed the description at 3 months, only the following formulations passed the description as a clear solution at the 6 months stability time point: (batch#-formulation#) 2-1 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 0% headspace oxygen), 2-2 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 5% headspace oxygen) and 3-1 (0.035 mg/ml sodium sulfite, 0.5 mg/ml EDTA, 0% headspace oxygen). All others showed precipitation at 6 months. Impurity D increased the most from the 3 month time point to the 6 month time point for all formulations. Formulation 3-1 with sulfite and EDTA present at 0% headspace oxygen (HO) had the lowest value at 6 months of those 3 formulations that passed the description without a precipitate.

[0102] FIG. 33 demonstrates the additional design of experiment result for impurity F (up to 6 months at 40°C/75%RH; 26.23 mg/ml DSP = 24 mg/ml DP) for the formulations without the presence of either sodium sulfite and/or EDTA at increasing levels of headspace oxygen (= HO: 0%, 5%, 10% and 15%): While all ten formulations passed the description at 3 months, only the following formulations passed the description as a clear solution at the 6 months stability time point: (batch#-formulation#) 2-1 (0.035 mg/ml sodium sulfite, 0 mg/ml

EDTA, 0% headspace oxygen), 2-2 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 5% headspace oxygen) and 3-1 (0.035 mg/ml sodium sulfite, 0.5 mg/ml EDTA, 0% headspace oxygen). All others showed precipitation at 6 months. The result shows that none of the formulations increase for impurity F beyond the 0.2 % threshold.

[0103] FIG. 34 demonstrates the additional design of experiment result for impurity G (up to 6 months at 40°C/75%RH; 26.23 mg/ml DSP = 24 mg/ml DP) for the formulations without the presence of either sodium sulfite and/or EDTA at increasing levels of headspace oxygen (= HO: 0%, 5%, 10% and 15%): While all ten formulations passed the description at 3 months, only the following formulations passed the description as a clear solution at the 6 months stability time point: (batch#-formulation#) 2-1 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 0% headspace oxygen), 2-2 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 5% headspace oxygen) and 3-1 (0.035 mg/ml sodium sulfite, 0.5 mg/ml EDTA, 0% headspace oxygen). All others showed precipitation at 6 months. The result shows that for impurity G, formulation 2-1 showed the lowest accumulation of all formulations at the 6 months time point.

[0104] FIG. 35 demonstrates the additional Design of experiment result for unidentified impurity (up to 6 months at 40°C/75%RH; 26.23 mg/ml DSP = 24 mg/ml DP): While all ten formulations passed the description at 3 months, only the following formulations passed the description as a clear solution at the 6 months stability time point: (batch#-formulation#) 2-1 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 0% headspace oxygen), 2-2 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 5% headspace oxygen) and 3-1 (0.035 mg/ml sodium sulfite, 0.5 mg/ml EDTA, 0% headspace oxygen). All others showed precipitation at 6 months. The result shows that the two sulfite formulations (of all three without precipitation at 6 months) lacking EDTA (2-1, 2-2) show the lowest values of the highest unidentified impurity.

[0105] FIG. 36 demonstrates the additional Design of experiment result for total impurities (up to 6 months at 40°C/75%RH; 26.23 mg/ml DSP = 24 mg/ml DP): While all ten formulations passed the description at 3 months, only the following formulations passed the description as a clear solution at the 6 months stability time point: (batch#-formulation#) 2-1 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 0% headspace oxygen), 2-2 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 5% headspace oxygen) and 3-1 (0.035 mg/ml sodium sulfite, 0.5 mg/ml EDTA, 0% headspace oxygen). All others showed precipitation at 6 months. The

total impurities are the sum total of all previous impurities (A, B, C, D, F, G, highest unidentified impurity) as well as additionally all other unidentified impurities (with different retention times) that are of lower value. The result shows that the two sulfite formulations (of all three without precipitation at 6 months) lacking EDTA (2-1, 2-2) show the lowest values lowest amount of total impurities. Therefore, for this formulation no EDTA is needed at a storage condition of 40°C/75%RH at 0 or 5% headspace oxygen

[0106] FIG. 37 demonstrates the DSP result and projection of additional Design of Experiment formulations 2-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 0% Oxygen headspace), 2-2 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 5% headspace oxygen) and 3-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0.5 mg/ml EDTA and 0% headspace oxygen). The projection with 4 measured (up to 6 months) data points shows for the formulations that the Dexamethasone Sodium Phosphate content is expected to be at 95% for 12 months (40°C/ 75%RH) for the formulation 2-1, while 2-2 and 3-1 are expected to be at a level of about 93% and 93.5% respectively. The result shows that EDTA is not necessary to achieve a better stability for the formulation.

[0107] FIG. 38 demonstrates the Impurity A result and projection of the additional Design of Experiment formulations 2-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 0% Oxygen headspace), 2-2 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 5% headspace oxygen) and 3-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0.5 mg/ml EDTA and 0% headspace oxygen). The projection with 4 measured (up to 6 months) data points shows for the formulations that the Impurity A level is expected to be below 1% for 12 months (40°C/ 75%RH) for the formulation 2-1 and 2-2, while for formulation 3-1 it is expected to reach 1% at about 9 months. The result shows that EDTA is not necessary to achieve a better stability for the formulation.

[0108] FIG. 39 demonstrates the Impurity C result and projection of the additional Design of Experiment formulations 2-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 0% Oxygen headspace), 2-2 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 5% headspace oxygen) and 3-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0.5 mg/ml EDTA and 0% headspace oxygen). The projection with 4 measured (up to 6 months) data points shows for the formulations that the Impurity C level is expected to be at 0.5% for 12 months

(40°C/ 75%RH) for the formulation 2-1, while being slightly below 0.5% for formulation 2-2 and 3-1 at this time point.

[0109] FIG. 40 demonstrates the Impurity D result and projection of additional Design of Experiment formulations 2-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 0% Oxygen headspace), 2-2 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 5% headspace oxygen) and 3-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0.5 mg/ml EDTA and 0% headspace oxygen). The projection with 4 measured (up to 6 months) data points shows that the Impurity D level is expected to be below 0.5% at 12 months (40°C/ 75%RH) for all 3 formulations.

[0110] FIG. 41 demonstrates the Impurity F result and projection of the additional Design of Experiment formulations 2-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 0% Oxygen headspace), 2-2 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 5% headspace oxygen) and 3-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0.5 mg/ml EDTA and 0% headspace oxygen). The projection with 4 measured (up to 6 months) data points shows that the Impurity F level is expected to be below 0.5% at 12 months (40°C/ 75%RH) for all 3 formulations.

[0111] FIG. 42 demonstrates the Impurity G result and projection of the additional Design of Experiment formulations 2-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 0% Oxygen headspace), 2-2 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 5% headspace oxygen) and 3-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0.5 mg/ml EDTA and 0% headspace oxygen). The projection with 4 measured (up to 6 months) data points shows that the Impurity G level is expected to be below 0.5% at 12 months (40°C/ 75%RH) for all 3 formulations.

[0112] FIG. 43 demonstrates the Unidentified Impurity result and projection of the additional Design of Experiment formulations 2-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 0% Oxygen headspace), 2-2 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 5% headspace oxygen) and 3-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0.5 mg/ml EDTA and 0% headspace oxygen). The projection with 4 measured (up to 6 months) data points shows that the level of the Unidentified Impurity is expected to be below 0.5% at

12 months (40°C/ 75%RH) for all 3 formulations. Moreover, the two formulations lacking EDTA (2-1 and 2-2) show an expected level even below 0.2% at 12 months.

[0113] FIG. 44 demonstrates the Total Impurites result and projection of additional Design of Experiment formulations 2-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 0% Oxygen headspace), 2-2 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 5% headspace oxygen) and 3-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0.5 mg/ml EDTA and 0% headspace oxygen). The projection with 4 measured (up to 6 months) data points shows that the level of the Total Impurites is expected to be below 3% at 12 months (40°C/ 75%RH) for the two formulations lacking the EDTA (2-1, 2-2), while reaching 3% for the formulation 3-1 with sulfite and EDTA present. The result demonstrates that EDTA is not necessary to increase the stability of the formulation.

[0114] FIG. 45 demonstrates the results for the impurities A and C of the additional design of experiment for increasing concentrations of Dexamethasone Sodium Phosphate (DSP). Six formulations with 3 varying levels of DSP (10, 30 and 45 mg/ml) with or without 0.5 mg/ml EDTA, respectively, were manufactured and put on stability (50 ml amber vial; 0, 1, 3, 6 months at 40°C/75%RH). All 6 formulations contained 5% headspace oxygen (95% nitrogen) and lacked sulfite. While there is a clear decrease of impurity C for all formulations over 6 months, there seems to be no clear trend for impurity A in the formulations including EDTA. For impurity A in the formulation lacking EDTA there is an initital increase visible that eventually stagnates,

[0115] FIG. 46 demonstrates the results for the impurities D and G of the additional design of experiment for increasing concentrations of Dexamethasone Sodium Phosphate (DSP). Six formulations with 3 varying levels of DSP (10, 30 and 45 mg/ml) with or without 0.5 mg/ml EDTA, respectively, were manufactured and put on stability (50 ml amber vial; 0, 1, 3, 6 months at 40°C/75%RH). All 6 formulations contained 5% headspace oxygen (95% nitrogen) and lacked sulfite. While there is a clear decrease of impurity G for all formulations over 6 months, there seems to be no clear trend for impurity D in the formulations lacking EDTA. For impurity D in the formulations including EDTA there is a visible increase over time up to ~0.2%.

[0116] FIG. 47 demonstrates the results for the Total Impurities of the additional design of experiment for increasing concentrations of Dexamethasone Sodium Phosphate (DSP). Six formulations with 3 varying levels of DSP (10, 30 and 45 mg/ml) with or without 0.5 mg/ml EDTA, respectively, were manufactured and put on stability (50 ml amber vial; 0, 1, 3, 6 months at 40°C/75%RH). All 6 formulations contained 5% headspace oxygen (95% nitrogen) and lacked sulfite. The formulations with the highest DSP content of 45 mg/ml still passed the description at 3 months, while all other failed and showed a precipitate. The result demonstrates that the formulations with an increasing DSP concentration form less total impurities over time, independent of the presence or absence of EDTA.

DETAILED DESCRIPTION

[0117] The present disclosure is directed to high concentration glucocorticoid containing pharmaceutical compositions comprising reduced levels of antioxidant acting preservatives. The present disclosure is based on the finding that use of a defined headspace volume to API ratio during distribution of the composition into packaging receptacles results in increased stability of the compositions in the presence of reduced levels of antioxidant preservatives. The pharmaceutical compositions of the present invention have several advantages over existing formulations. Given that antioxidant preservatives have been found to be associated with patient sensitivity and toxicity, pharmaceutical compositions comprising lower levels of such preservatives, while retaining stability of the composition at 2^0C to 40^0C, is highly desirable.

[0118] That is, the present disclosure is directed to aqueous pharmaceutical formulations comprising a glucocorticoid. The aqueous pharmaceutical formulations comprise reduced levels of preservative, which may be antioxidant acting preservatives. The aqueous pharmaceutical formulations of the present invention have several advantages over existing formulations. Given that preservatives have been found to be associated with patient sensitivity and toxicity, pharmaceutical formulations comprising lower levels of such preservatives, while retaining stability of the formulation, are highly desirable.

[0119] The present invention is based in part on the finding that use of a defined headspace volume (ml) to glucocorticoid (mg) ratio during packaging of the formulation into containers results in increased stability of the formulation, even with reduced or no amount of preservative. Accordingly, in some embodiments of the aqueous pharmaceutical formulations comprising a glucocorticoid, the formulation is packaged in a container with a headspace

volume (ml) to total glucocorticoid content (mg) ratio of 0.007 or less. In some embodiments the headspace volume (ml) to total glucocorticoid content (mg) ratio may be 0.0065 or less, 0.0060 or less, 0.00588 or less, 0.0055 or less, 0.0050 or less, 0.0045 or less, 0.0040 or less, 0.0035 or less, 0.0030 or less, 0.0025 or less, 0.0020 or less, 0.0015 or less, or 0.0010 or less. In some preferred embodiments, the headspace volume (ml) to total glucocorticoid content (mg) ratio may be 0.00588 or less.

[0120] In some embodiments of the aqueous pharmaceutical formulations comprising a glucocorticoid, the formulation is packaged in a container with a headspace volume (ml) to total glucocorticoid content (mg) ratio of between about 0.0046 to about 0.0099. In some embodiments the headspace volume (ml) to total glucocorticoid content (mg) ratio may be between about 0.003 and 0.007, or between about 0.004 and 0.006. In some embodiments the headspace volume (ml) to total glucocorticoid content (mg) ratio may be between about 0.001 and 0.00588.

[0121] Those skilled in the art can easily calculate equivalent concentrations of dexamethasone for a given glucocorticoid, as outlined in detail below. Accordingly, in some cases the headspace volume (ml) to total glucocorticoid content (mg) ratio may be expressed as a ratio of the headspace volume (ml) to glucocorticoid content (mg), wherein the glucocorticoid content is expressed as an equivalent content of dexamethasone (mg). That is, in some embodiments, the headspace volume (ml) to total glucocorticoid content (mg) ratio may be, or may be expressed as, a headspace volume (ml) to dexamethasone content (mg) ratio.

[0122] Means for determing headspace volume in a container are well known to those skilled in the art. For example, during packaging the headspace volume can be measured by the following calculation: (vial brim volume – stopper volume – fluid fill volume); or, by adding a liquid and measuring the volume when all gas has been replaced.

[0123] In some embodiments of the aqueous pharmaceutical formulations comprising a glucocorticoid, the formulation may be packaged in a container with a total sulfite content (mg) to total glucocorticoid content (mg) ratio of 0.0040 or less, 0.0035 or less, 0.0030 or less, 0.0025 or less, 0.0020 or less, 0.0015 or less, 0.00146 or less, or 0.0010 or less. In some preferred embodiments, the formulation may be packaged in a container with a total sulfite content (mg) to total glucocorticoid content (mg) ratio of 0.00150 or less. In some particularly

preferred embodiments, the formulation may be packaged in a container with a total sulfite content (mg) to total glucocorticoid content (mg) ratio of 0.00146 or less.

[0124] In some embodiments of the aqueous pharmaceutical formulations comprising a glucocorticoid, the formulation may be packaged in a container with a sulfite content (mg): glucocorticoid content (mg) : headspace volume (mg) ratio of 0.000203 or less.

[0125] In some embodiments of the aqueous pharmaceutical formulations comprising a glucocorticoid, the formulation may be packaged in a container with a ((sulfite (mg) : glucocorticoid content (mg)) x headspace volume (mg)) value of 0.01050 or less.

[0126] In some embodiments the headspace volume may be about 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 ml. In some embodiments the headspace volume may be less than about 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 ml. In some preferred embodiments the headspace volume may be or may be less than about 8 ml. In other preferred embodiments the headspace volume may be or may be less than about 7.2 ml.

[0127] In some embodiments, the headspace volume may be about 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 % of the total container volume. In some embodiments, the headspace volume may be less than about 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 % of the total container volume.

[0128] In some embodiments the headspace volume may comprise about 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 % oxygen. In some embodiments the headspace volume may comprise less than about 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 % oxygen. In some preferred embodiments the headspace volume may comprise about 5% oxygen or may comprise less than about 5% oxygen. In other preferred embodiments the headspace volume may comprise about 0% oxygen.

[0129] Means for determing headspace oxygen levels in a given headspace volume are well known to those skilled in the art. For example, headspace oxygen levels may be measured by conventional destructive techniques, such as electrochemical methods or gas chromatography, or by non-destructive methods such as laser-based Frequency Modulation Spectroscopy (Pharmaceutical Technology, July 2002; Lighthouse Instruments Application Note 102).

[0130] The aqueous pharmaceutical formulations of the invention advantageously comprise lower amounts of preservative (such as an antioxidant or antimicrobial) than known glucocorticoid formulations. Accordingly, in some embodiments, the formulation may (or may not) comprise a pharmaceutically acceptable preservative. In some embodiments, the formulation may comprise a sulfite preservative present in a concentration of less than about 1 mg/ml; a paraben preservative present in a concentration of less than about 0.2 mg/ml; creatinine present in a concentration of less than about 8 mg/ml; and/or benzethonium chloride present in a concentration of less than about 0.1 mg/ml. In some preferred embodiments, the total concentration of preservative in the formulation may be less than about 0.1 mg/ml.

[0131] In some embodiments, the concentration of preservative may be about 0.09 mg/ml, about 0.08 mg/ml, about 0.07 mg/ml, about 0.06 mg/ml, about 0.05 mg/ml, about 0.04 mg/ml, about 0.035 mg/ml, about 0.03 mg/ml, about 0.02 mg/ml, or about 0.01 mg/ml. In some embodiments, the concentration of preservative may be less than about 0.09 mg/ml, less than about 0.08 mg/ml, less than about 0.07 mg/ml, less than about 0.06 mg/ml, less than about 0.05 mg/ml, less than about 0.04 mg/ml, less than about 0.035 mg/ml, less than about 0.03 mg/ml, less than about 0.02 mg/ml, or less than about 0.01 mg/ml. In some preferred embodiments, the concentration of preservative may be about 0.07 mg/ml, or may be less than about 0.07 mg/ml. In other preferred embodiments, the concentration of preservative may be about 0.035 mg/ml, or may be less than about 0.035 mg/ml.

[0132] In some particularly preferred embodiments the concentration of preservative may be 0 mg/ml. That is, in some particularly preferred embodiments the formulation does not comprise a preservative.

[0133] As outlined above, the pharmaceutical formulations of the invention may (or may not) comprise a pharmaceutically acceptable preservative (such as an antioxidant or antimicrobial) additive to maintain the stability of the formulation. Antioxidants are added in amounts that are reduced as compared to levels typically employed in known glucocorticoid containing formulations – thereby reducing the toxicity and adverse side effects associated with use of such antioxidant preservatives.

[0134] As used herein, antioxidants (antioxidant preservatives) are those excipients known to those skilled in the art to delay or inhibit the oxidation process of molecules, thereby increasing the stability of the composition. Such antioxidants include, but are not limited to, ascorbic acid, acetylcysteine, butylhydroxyanisol, cysteine hydrochloride, dithionite sodium, gentisic acid, glutamate monosodium, glutathione, formaldehyde sulfoxylate sodium, methionine, monothioglycerol, propyl gallate, sulfites, sodium thioglycolate, α-thioglycerol, tocopherol alpha, alpha tocopherol hydrogen succinate, vitamin A, vitamin C, vitamin E, beta-carotene, lycopene, lutein, selenium, manganese, zeaxanthin, flavonoids, flavones, catechins, polyphenols, and phytoestrogens, and thioglycolate sodium. In some cases the antioxidant (antioxidant preservative) is a sulfite. Such sulfites relate to, but are not limited to, sodium sulfite (anhydrous) (Na_2SO_3), sodium bisulfite ($NaHSO_3$), potassium bisulfite ($KHSO_3$), potassium metabisulfite ($K_2S_2O_5$) and sodium metabisulfite ($Na_2S_2O_5$).

[0135] Thus, in some embodiments of the pharmaceutical formulations of the invention, the preservative may be a sulfite, a paraben, benzyl alcohol, benzethonium chloride, propylene glycol, and / or creatinine. In some embodiments, the sulfite may be sodium sulfite (anhydrous), sodium bisulfite, sodium metabisulfite, potassium bisulfite, and / or potassium metabisulfite. In some embodiments, the paraben may be methylparaben, propylparaben, ethylparaben, butylparaben, isopropylparaben and / or isobutylparaben. In some embodiments, the paraben may be methylparaben and / or propylparaben.

[0136] In some embodiments, the concentration of sulfite preservative may be about 1 mg/ml or less than about 1 mg/ml. In some embodiments, the concentration of sulfite preservative may be about 0.9 mg/ml, about 0.8 mg/ml, about 0.7 mg/ml, about 0.6 mg/ml, about 0.5 mg/ml, about 0.4 mg/ml, about 0.3 mg/ml, about 0.2 mg/ml, or about 0.1 mg/ml. In some embodiments, the concentration of sulfite preservative may be less than about 0.9 mg/ml, less than about 0.8 mg/ml, less than about 0.7 mg/ml, less than about 0.6 mg/ml, less than about 0.5 mg/ml, less than about 0.4 mg/ml, less than about 0.3 mg/ml, less than about 0.2 mg/ml, or less than about 0.1 mg/ml. In some embodiments, the concentration of sulfite preservative may be about 0.09 mg/ml, about 0.08 mg/ml, about 0.07 mg/ml, about 0.06 mg/ml, about 0.05 mg/ml, about 0.04 mg/ml, about 0.03 mg/ml, about 0.02 mg/ml, or about 0.01 mg/ml. In some embodiments, the concentration of sulfite preservative may be less than about 0.09 mg/ml, less than about 0.08 mg/ml, less than about 0.07 mg/ml, less than about 0.06 mg/ml, less than about 0.05 mg/ml, less than about 0.04 mg/ml, less than about 0.03 mg/ml, less than about 0.02

mg/ml, or less than about 0.01 mg/ml. In some preferred embodiments the concentration of sulfite preservative may be 0 mg/ml. That is, in some preferred embodiments the formulation does not comprise a sulfite preservative.

[0137] In some embodiments, the concentration of paraben preservative may be about 0.2 mg/ml or less than about 0.2 mg/ml. In some embodiments, the concentration of paraben preservative may be about 0.1 mg/ml or less than about 0.1 mg/ml. In some embodiments, the concentration of paraben preservative may be about 0.09 mg/ml, about 0.08 mg/ml, about 0.07 mg/ml, about 0.06 mg/ml, about 0.05 mg/ml, about 0.04 mg/ml, about 0.03 mg/ml, about 0.02 mg/ml, or about 0.01 mg/ml. In some embodiments, the concentration of paraben preservative may be less than about 0.09 mg/ml, less than about 0.08 mg/ml, less than about 0.07 mg/ml, less than about 0.06 mg/ml, less than about 0.05 mg/ml, less than about 0.04 mg/ml, less than about 0.03 mg/ml, less than about 0.02 mg/ml, or less than about 0.01 mg/ml. In some preferred embodiments the concentration of paraben preservative may be 0 mg/ml. That is, in some preferred embodiments the formulation does not comprise a paraben preservative.

[0138] In some embodiments, the concentration of creatinine may be about 8 mg/ml, or may be less than about 8 mg/ml. In some embodiments, the concentration of creatinine may be about 7 mg/ml, about 6 mg/ml, about 5 mg/ml, about 4 mg/ml, about 3 mg/ml, about 2 mg/ml, or about 1 mg/ml. In some embodiments, the concentration of creatinine may be less than about 7 mg/ml, less than about 6 mg/ml, less than about 5 mg/ml, less than about 4 mg/ml, less than about 3 mg/ml, less than about 2 mg/ml, or less than about 1 mg/ml. In some embodiments, the concentration of creatinine may be about 0.9 mg/ml, about 0.8 mg/ml, about 0.7 mg/ml, about 0.6 mg/ml, about 0.5 mg/ml, about 0.4 mg/ml, about 0.3 mg/ml, about 0.2 mg/ml, or about 0.1 mg/ml. In some embodiments, the concentration of creatinine may be less than about 0.9 mg/ml, less than about 0.8 mg/ml, less than about 0.7 mg/ml, less than about 0.6 mg/ml, less than about 0.5 mg/ml, less than about 0.4 mg/ml, less than about 0.3 mg/ml, less than about 0.2 mg/ml, or less than about 0.1 mg/ml. In some embodiments, the concentration of creatinine may be about 0.09 mg/ml, about 0.08 mg/ml, about 0.07 mg/ml, about 0.06 mg/ml, about 0.05 mg/ml, about 0.04 mg/ml, about 0.03 mg/ml, about 0.02 mg/ml, or about 0.01 mg/ml. In some embodiments, the concentration of creatinine may be less than about 0.09 mg/ml, less than about 0.08 mg/ml, less than about 0.07 mg/ml, less than about 0.06 mg/ml, less than about 0.05 mg/ml, less than about 0.04 mg/ml, less than about 0.03 mg/ml, less than about 0.02 mg/ml, or less than about 0.01 mg/ml. In some preferred embodiments the

concentration of creatinine may be 0 mg/ml. That is, in some preferred embodiments the formulation does not comprise creatinine.

[0139] In some embodiments, the concentration of benzethonium chloride may be about 0.1 mg/ml or less than about 0.1 mg/ml. In some embodiments, the concentration of benzethonium chloride may be about 0.09 mg/ml, about 0.08 mg/ml, about 0.07 mg/ml, about 0.06 mg/ml, about 0.05 mg/ml, about 0.04 mg/ml, about 0.03 mg/ml, about 0.02 mg/ml, or about 0.01 mg/ml. In some embodiments, the concentration of benzethonium chloride may be less than about 0.09 mg/ml, less than about 0.08 mg/ml, less than about 0.07 mg/ml, less than about 0.06 mg/ml, less than about 0.05 mg/ml, less than about 0.04 mg/ml, less than about 0.03 mg/ml, less than about 0.02 mg/ml, or less than about 0.01 mg/ml. In some preferred embodiments the concentration of benzethonium chloride may be 0 mg/ml. That is, in some preferred embodiments the formulation does not comprise benzethonium chloride.

[0140] The aqueous pharmaceutical formulations of the invention may advantageously comprise lower amounts of a chelating agent than known glucocorticoid formulations. Chelating agents are commonly included in pharmaceutical formulations to sequester and decrease the reactivity of metal ions that may be present in the formulation.

[0141] Accordingly, in some embodiments, the formulations of the invention may (or may not) comprise a chelating agent. In some embodiments, the formulation may comprise a chelating agent, wherein the concentration of chelating agent is or is less than about 0.50 mg/ml. In some embodiments the concentration of chelating agent may be about 0.45 mg/ml, about 0.40 mg/ml, about 0.35 mg/ml, about 0.30 mg/ml, about 0.25 mg/ml, about 0.20 mg/ml, about 0.15 mg/ml, about 0.10 mg/ml, or about 0.05 mg/ml. In some embodiments the concentration of chelating agent may be less than about 0.45 mg/ml, less than about 0.40 mg/ml, less than about 0.35 mg/ml, less than about 0.30 mg/ml, less than about 0.25 mg/ml, less than about 0.20 mg/ml, less than about 0.15 mg/ml, less than about 0.10 mg/ml, or less than about 0.05 mg/ml. In some preferred embodiments the concentration of chelating agent may be 0 mg/ml. That is, in some preferred embodiments the formulation does not comprise a chelating agent. In some preferred embodiments the formulation does not comprise disodium edetate (disodium EDTA).

[0142] Possible chelating agents include, but are not limited to, calcium disodium EDTA 0.01-0.1% (EDTA = Ethylenediaminetetra acetic acid or Edetate), Disodium EDTA 0.01-0.11%,

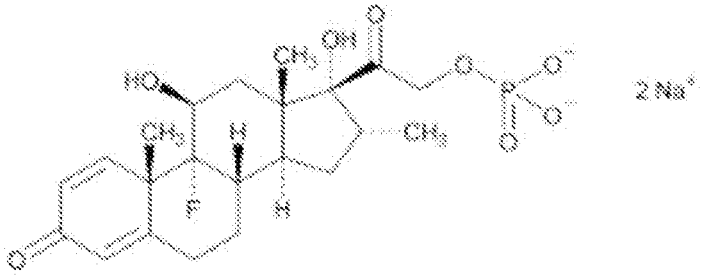
Sodium EDTA 0.20%, Calcium Versetamide Sodium 2.84%, Calteridol 0.023%, and DTPA 0.04-1.2% (Diethylenetriaminepenta acetic acid). Other chelating agents include, but are not limited to, acetic acid, citric acid, ascorbic acid, lactic acid, edetic acid, nitriloacetic acid, dipicolinic acid, gadoteric acid, pentetic acid, gluconic acid, L-tartaric acid, thiosulfuric acid, emeramide, poliglusam, acteoside, thenoyltrifluoroacetone, tagatose, tetrathiomolybdate, alanosine, dimercaprol, triethyltetramine, deferiprone, calcium acetate, succimer, sevelamer, deferoxamine, penicillamine, tolevamer, deferasirox, 1,10-phenanthroline, and ditiocarb. In some embodiments, the chelating agent may be one or more of these. In some embodiments, the chelating agent may be ethylenediamine, ethylenediaminetetraacetic acid (EDTA), sodium edetate, disodium edetate, tetrasodium edetate, calcium disodium edetate, calcium versetamide sodium, calteridol, and / or diethylenetriaminepenta acetic acid (DPTA). In some preferred embodiments, the chelating agent may be disodium edetate (disodium EDTA).

[0143] As used herein, the term glucocorticoid includes glucocorticoid receptor agonists and any compound that binds to the glucocorticoid receptor. Such compounds relate to, but are not limited to, dexamethasone, dexamethasone containing agents, hydrocortisone, methylprednisolone, prednisone, prednisolone, prednylidene, cortisone, budesonide, betamethasone and beclomethasone. Other glucocorticoids include mometasone furoate, Triamcinolone Acetonide and methylprednisone. Glucocorticoids further include glucocorticoid receptor modulating agonists. Additionally, selective glucocorticoid receptor agonists or modulators may be used in the pharmaceutical formulations disclosed herein. Such agonists or modulators include for example, selective glucocorticoid receptor modulators (SEGRMs) and selective glucocorticoid receptor agonists (SEGRAs). Glucocorticoids, glucocorticoid receptor modulators and selective glucocorticoid receptor agonists (SEGRAs) that may be utilized in the herein disclosed formulations and methods are well known to those skilled in the art.

[0144] The term glucocorticoid-receptor modulating agents as used herein non-exclusively relates to glucocorticoid receptor agonists or glucocorticoid receptor modulators including but not limited to: compound A [CpdA; (2-((4-acetophenyl)-2-chloro-N-methyl)ethylammoniumchloride)] and N-(4-methyl-1-oxo-1H-2,3-benzoxazine-6-yl)-4-(2,3-dihydrobenzofuran-7-yl)-2-hydroxy-2 (trifluoromethyl)-4-methylpentanamide (ZK216348), AL-438, Mapracorat, LGD-5552 , RU 24858, Fosdagrocorat, PF-802, Compound 10, MK5932, C108297, LGD5552, and ORG 214007-0.

[0145] Glucocorticoids and glucocorticoid-receptor (GR) modulating agents exert their effects through both membrane glucocorticoid receptors and cytoplasmic GRs which activate or repress gene expression. Some of the desirable lymphodepletion effects of the glucocorticoids and GR modulating agents appear to be mediated via membrane GRs or other non-genomic effects in addition to their genomic effects. Interestingly, co-treatment with dexamethasone has been shown to be able to reduce glucocorticoid resistance (Serafin *et al.,* 2017).

[0146] In some embodiments of the aqueous pharmaceutical formulations comprising a glucocorticoid, the glucocorticoid is selected from the group consisting of dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, prednylidene, cortisone, budesonide, betamethasone and beclomethasone. In some preferred embodiments the glucocorticoid comprises dexamethasone, which may be selected from the group consisting of dexamethasone base, dexamethasone sodium phosphate, dexamethasone hemisuccinate, dexamethasone sodium succinate, dexamethasone succinate, and dexamethasone acetate. In some preferred embodiments the glucocorticoid is dexamethasone sodium phosphate. In some preferred embodiments the glucocorticoid is dexamethasone having the following formula (dexamethasone phosphate (as sodium)):



[0147] Dexamethasone phosphate (as sodium) is a white or slightly yellow, very hygroscopic, crystalline powder. It is odourless or has a slight odour of alcohol. Dexamethasone phosphate (as sodium) is soluble 1 in 2 in water, slightly soluble in alcohol, practically insoluble in chloroform and ether, and very slightly soluble in dioxan.

[0148] The present invention is based in part on the finding that the glucocorticoid Dexamethasone Sodium Phosphate (DSP), when present in high concentrations in an aqueous formulation, is increasingly self-protective against degradative processeses like hydrolyzation

and oxidization. Accordingly, in some embodiments of the aqueous pharmaceutical formulations comprising a glucocorticoid, the concentration of glucocorticoid may be about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 26.23, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, or 45 mg/ml. In some embodiments, the concentration of glucocorticoid may be at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, or 45 mg/ml. In some particularly preferred embodiments the concentration of glucocorticoid may be about 24 mg/ml, or may be at least about 24 mg/ml. In other preferred embodiments the concentration of glucocorticoid may be about 26.23 mg/ml, or may be at least about 26.23 mg/ml. In other preferred embodiments the concentration of glucocorticoid may be about 30 mg/ml, or may be at least about 30 mg/ml. In other preferred embodiments the concentration of glucocorticoid may be about 45 mg/ml, or may be at least about 45 mg/ml.

[0149] In some embodiments of the aqueous pharmaceutical formulations comprising a glucocorticoid, the concentration of glucocorticoid may be less than about 500, 457, 450, 400, 350, 300, 250, 200, 150, or 100 mg/ml. In some preferred embodiments, the concentration of glucocorticoid may be less than about 457 mg/ml. In other preferred embodiments, the concentration of glucocorticoid may be less than about 250 mg/ml.

[0150] Those skilled in the art can easily calculate equivalent concentrations of glucocorticoids or glucocorticoid receptor modulating agents, for example using publicly available corticoid conversion algorithms. Those skilled in the art know, for example, that 10, 26.23, 30 and 45 mg/ml of dexamethasone sodium phosphate (DSP) is equivalent to 9.15, 24, 27.45 and 41.17 mg/ml respectively of dexamethsone phosphate (DP). Similarly, 26.23 and 45 mg/ml of dexamethasone sodium phosphate (DSP) is equivalent to 19.94 and 34.2 mg/ml respectively of dexamethasone. Thus, in some cases, the concentration of a glucocorticoid may be expressed as a concentration equivalent to a given concentration of another glucocorticoid – e.g., "a concentration equivalent to a given concentration of dexamethasone". For example, 9.15 mg/ml of dexamethsone phosphate may be alternatively expressed as "a concentration of dexamethsone phosphate equivalent to 10 mg/ml of dexamethasone sodium phosphate" and vice versa. As another example, 34.2 mg/ml of dexamethasone may be alternatively expressed as "a concentration of dexamethsone equivalent to 45 mg/ml of dexamethasone sodium phosphate".

[0151] In some embodiments, the concentration of glucocorticoid may be between about 4.4 mg/ml to about 1000 mg/ml. In some embodiments the glucocorticoid is dexamethasone phosphate in a concentration between about 4.4 mg/ml and about 457 mg/ml DP (dexamethasone phosphate), more preferably between about 24 mg/ml and about 457 mg/ml DP). In some embodiments the glucocorticoid is dexamethasone phosphate in a concentration between about 24 mg/ml and about 450 mg/ml DP, between about 24 mg/ml and about 400 mg/ml DP, between about 24 mg/ml and about 350 mg/ml DP, between about 24 mg/ml and about 300 mg/ml DP, more preferably between about 24 mg/ml and about 250 mg/ml DP.

[0152] In some embodiments, the pH of the formulation may be between about 7.0 to about 8.2, about 7.2 to about 8.0, about 7.3 to about 7.9, or between about 7.4 to about 7.8, In some preferred embomdiments, the pH of the formulation may be between about 7.4 to about 7.8. In some preferred embodiments, the pH of the formulation may be about 7.6.

[0153] In addition to the glucocorticoid, preservative (which may be an antioxidant preservative), and chelating agent outlined above, additional components well known to those of skill in the art may be included in the pharmaceutical formulations of the invention. Pharmaceutical formulations may be prepared using a pharmaceutically acceptable “carrier” composed of materials that are considered safe and effective. "Pharmaceutically acceptable" refers to molecular entities and compositions that are "generally regarded as safe", *e.g.*, that are physiologically tolerable and do not typically produce an allergic or similar untoward reaction, such as gastric upset and the like, when administered to a human. In some embodiments, this term refers to molecular entities and compositions approved by a regulatory agency of the US federal or a state government, as the GRAS list under section 204(s) and 409 of the Federal Food, Drug and Cosmetic Act, that is subject to premarket review and approval by the FDA or similar lists, the U.S. Pharmacopeia or another generally recognized pharmacopeia for use in animals, and more particularly in humans.

[0154] The term “carrier” relates to, but is not limited to, diluents, binders, lubricants, and disintegrants. Those with skill in the art are familiar with such pharmaceutical carriers and methods of compounding pharmaceutical compositions and formulations using such carriers.

[0155] The pharmaceutical formulations of the invention may (or may not) include one or more excipients, *e.g.*, solvents, solubility enhancers, suspending agents, buffering agents,

isotonicity agents, stabilizers, and antioxidants or antimicrobial preservatives. The IID lists the highest amount of the excipient per unit dose in each dosage form in which it is used. The amounts shown for maximum potency do not reflect the maximum daily intake (MDI) of the excipient unless the maximum daily dose of the product that is the basis for the listing is only a single unit. When used, the excipients of the compositions will not adversely affect the stability, bioavailability, safety, and/or efficacy of the active ingredients, ie., glucocorticoids, used in the formulation. Thus, formulations are provided wherein there is no incompatibility between any of the components of the dosage form. Excipients may be selected from the group consisting of buffering agents, solubilizing agents, tonicity agents, chelating agents, antioxidants, antimicrobial agents, and preservatives. In some embodiments, the pharmaceutical formulations may comprise a buffer (buffering agent). In some embodiments, the buffer may be sodium citrate. In some preferred embodiments, the concentration of buffer may be about 10 mg/ml.

[0156] The present disclosure is based in part on the finding that use of a defined headspace volume (ml) to glucocorticoid (mg) ratio during the packaging of the formulation into a container results in a maintained stability of the formulation close to its state directly after manufacture. In some embodiments the container may be a vial, ampoule, solvent reservoir, storage bottle, medical bottle, syringe, or bottle.

[0157] Those skilled in the art will appreciate that formulations packaged in smaller volumes are easier to stabilize, and therefore require less preservative. For example, formulations packaged in smaller volumes are easier to stabilize against oxygen (oxidative degradation). Surprisingly, use of the defined headspace volume (ml) to glucocorticoid (mg) ratio of the present invention results in increased stability of aqueous formulations, with reduced or no amount of preservative, even in large volume containers. Accordingly, in some emodiments, the volume of the container may be about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 51, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 ml. In some embodiments, the volume of the container may be at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 51, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 ml. In some preferred embodiments, the volume of the container may be about 59 ml, or may be at least about 59 ml. In some preferred embodiments, the volume of the container may be about 51 ml, or may be at least about 51 ml. In other preferred embodiments, the volume of the container may be about 50 ml, or may be at least about 50 ml. In some embodiments the volume of pharmaceutical formulation packaged

in the container may be at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 ml. In some preferred embodiments the volume of pharmaceutical formulation packaged in the container may be about 43 ml, or may be at least about 43 ml. In some preferred embodiments the volume of pharmaceutical formulation packaged in the container may be about 50 ml, or may be at least about 50 ml. In some preferred embodiments the volume of pharmaceutical formulation packaged in the container may be about 51 ml, or may be at least about 51 ml.

[0158] The aqueous pharmaceutical formulations of the invention advantageously comprise low or no amounts of preservative and / or chelating agent while retaining comparable stability to known preservative-containing glucocorticoid formulations.

[0159] Accordingly, in some embodiments the aqueous pharmaceutical formulations of the invention remain stable for at least about 18, 24, 36, or 48 months following manufacture. In some embodiments the aqueous pharmaceutical formulations remain stable for at least about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, or 48 months following manufacture. Accordingly, stability of the formulation may be assessed at 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, or 48 months after manufacture. In some preferred embodiments, stability of the formulation may be assessed at 18, 24, 36, or 48 months after manufacture.

[0160] In some embodiments the aqueous pharmaceutical formulations have a shelf-life of at least about 18, 24, 36, or 48 months following manufacture. In some embodiments the aqueous pharmaceutical formulations have a shelf-life of at least about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, or 48 months following manufacture.

[0161] Means for determing stability and shelf-life of aqueous pharmaceutical formulations comprising a glucocorticoid are well known to those skilled in the art. For example, stability and shelf-life of a formulation may be determined by assaying quantitative chemical attributes of the formulation such as levels of the glucocorticoid API or its degradation products.

[0162] In some embodiments, stability is determined following storage of the formulation between 2°C to 40°C. In some embodiments, stability is determined following storage of the formulation between 15°C to 40°C. In some preferred embodiments, stability is determined following storage of the formulation between 20°C to 40°C. In some preferred embodiments, stability is determined following storage of the formulation between 15°C to 20°C. In some preferred embodiments, stability is determined following storage of the formulation at room temperature. In some preferred embodiments, stability is determined following storage of the formulation at 25°C. In some preferred embodiments, stability is determined following storage of the formulation at 40°C.

[0163] In some embodiments, stability is determined following storage of the formulation between 40 to 80 % relative humidity (RH). In some embodiments, stability is determined following storage of the formulation between 50 to 70 % RH. In some preferred embodiments, stability is determined following storage of the formulation at 60 % RH. In some preferred embodiments, stability is determined following storage of the formulation at 75 % RH. In some preferred embodiments, stability is determined following storage of the formulation at 25°C, 60 % RH. In some preferred embodiments, stability is determined following storage of the formulation at 40°C, 75 % RH.

[0164] In some embodiments, stability is determined by determining the degree of degradation of the glucocorticoid API in the formulation. Means for determing the amount of glucocorticoid API in a formulation are well known to those skilled in the art – for example, high performance liquid chromatography coupled to UV spectrometry (HPLC-UV) methods, or ultra performance liquid chromatography (UPLC) methods. In some embodiments, the formulation exhibits less than about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2, 3.4, 3.6, 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, 5.0 % degradation of the glucocorticoid API. In some preferred embodiments, the formulation exhibits less than about 5.0 % degradation of the glucocorticoid API.

[0165] In some embodiments, the amount of glucocorticoid in the formulation is maintained above about 95.0, 95.2, 95.4, 95.6, 96.0, 96.2, 96.4, 96.6, 96.8, 97.0, 97.2, 97.4, 97.6, 98.0, 98.2, 98.4, 98.6, 98.8, 99.0, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, or 99.9 % as compared to the date of manufacture. In some preferred embodiments, the amount of

glucocorticoid in the formulation is maintained above about 95.0 % as compared to the date of manufacture.

[0166] In some embodiments, the amount of glucocorticoid in the formulation is maintained between about ± 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2, 3.4, 3.6, 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, or 5.0 % as compared to the date of manufacture. In some preferred embodiments, the amount of glucocorticoid in the formulation is maintained between about ± 5.0 % as compared to the date of manufacture.

[0167] In some embodiments, stability is determined by determining the degree of change in pH of the formulation. Means for determing the pH of a formulation are well known to those skilled in the art. In some embodiments, the formulation exhibits less than about ± 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.2, 1.4, 1.6, 1.8, or 2.0 change in pH. In some preferred embodiments, the formulation exhibits less than about ± 0.5 change in pH. In some preferred embodiments, the formulation exhibits less than about ± 0.2 change in pH.

[0168] In some embodiments, the glucocorticoid is dexamethasone sodium phosphate and stability is determined by determining the degree of accumulation of impurity A (9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-3,20-dione (dexamethasone)) in the formulation. Means for determing the amount of impurity A in a formulation are well known to those skilled in the art. In some embodiments, the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity A. In some preferred embodiments, the formulation exhibits less than about 0.50 % accumulation of impurity A. In other preferred embodiments, the formulation exhibits less than about 1.0% accumulation of impurity A.

[0169] In some embodiments, the glucocorticoid is dexamethasone sodium phosphate and stability is determined by determining the degree of accumulation of impurity B (9-fluoro-11β,17-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-21-yl dihydrogen phosphate (betamethasone phosphate)) in the formulation. Means for determing the amount of impurity B in a formulation are well known to those skilled in the art. In some embodiments, the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity B. In

some preferred embodiments, the formulation exhibits less than about 0.50 % accumulation of impurity B.

[0170] In some embodiments, the glucocorticoid is dexamethasone sodium phosphate and stability is determined by determining the degree of accumulation of impurity C in the formulation. Means for determing the amount of impurity C in a formulation are well known to those skilled in the art. In some embodiments, the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity C. In some preferred embodiments, the formulation exhibits less than about 0.50 % accumulation of impurity C.

[0171] In some embodiments, the glucocorticoid is dexamethasone sodium phosphate and stability is determined by determining the degree of accumulation of impurity D in the formulation. Means for determing the amount of impurity D in a formulation are well known to those skilled in the art. In some embodiments, the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity D. In some preferred embodiments, the formulation exhibits less than about 0.50 % accumulation of impurity D.

[0172] In some embodiments, the glucocorticoid is dexamethasone sodium phosphate and stability is determined by determining the degree of accumulation of impurity E in the formulation. Means for determing the amount of impurity E in a formulation are well known to those skilled in the art. In some embodiments, the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity E. In some preferred embodiments, the formulation exhibits less than about 0.50 % accumulation of impurity E.

[0173] In some embodiments, the glucocorticoid is dexamethasone sodium phosphate and stability is determined by determining the degree of accumulation of impurity F in the formulation. Means for determing the amount of impurity F in a formulation are well known to those skilled in the art. In some embodiments, the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity F. In some preferred embodiments, the formulation exhibits less than about 0.50 % accumulation of impurity F.

[0174] In some embodiments, the glucocorticoid is dexamethasone sodium phosphate and stability is determined by determining the degree of accumulation of impurity G in the formulation. Means for determing the amount of impurity G (9-fluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid) in a formulation are well known to those skilled in the art. In some embodiments, the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity G. In some preferred embodiments, the formulation exhibits less than about 0.50 % accumulation of impurity G.

[0175] In some embodiments, stability is determined by determining the degree of accumulation of unspecified impurities in the formulation. Means for determing the amount of unspecified impurities in a formulation are well known to those skilled in the art. In some embodiments, the formulation exhibits less than about 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19 0.20, 0.21, 0.22, 0.23, 0.24, 0.25, 0.26, 0.27, 0.28, 0.29, or 0.30 % accumulation of unspecified impurities. In some preferred embodiments, the formulation exhibits less than about 0.20 % accumulation of unspecified impurities.

[0176] In some embodiments, stability is determined by determining the degree of accumulation of total impurities in the formulation. Means for determing the amount of total impurities in a formulation are well known to those skilled in the art. In some embodiments, the formulation exhibits less than about 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2, 3.4, 3.6, 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, or 5.0 % accumulation of total impurities. In some preferred embodiments, the formulation exhibits less than about 3.0 % accumulation of total impurities.

[0177] Some specific embodiments of the aqueous pharmaceutical formulations of the invention are as follows.

[0178] In some embodiments, the stability achieved by the composition may be such that the DSP assay is maintained at 94% or higher, preferably 97% or higher, after storage at 25 degree Celsius and 60% RH for 24 months, or for 29 months. In some embodiments, the stability achieved by the composition may be such that the DSP assay is maintained at 94% or higher,

preferably 96% or higher, more preferably 97% or higher, after storage at 40 degree Celsius and 75% RH for 6 months. In some embodiments, the stability achieved by the composition may be such that the level of Impurity A remains not more than 0.35%, preferably below 0.25%, more preferably below 0.20% after storage at 25 degree Celsius and 60% RH for 24 months, or for 29 months.

[0179] In some embodiments, the stability achieved by the composition may be such that the level of Impurity A (impurity A (dexamethasone)) remains no greater than 2.0% and below 1.5%, preferably below 0.9%, more preferably below 0.8%, after storage at 40 degree Celsius and 75% RH for 6 months.

[0180] In some embodiments, the stability achieved by the composition may be such that the level of Impurity B (betamethasone sodium phosphate) remains not more than 0.3%, preferably below 0.2%, more preferably below 0.1% after storage at 25 degree Celsius and 60% RH for 24 months, or 29 months. In some embodiments, the stability achieved by the composition may be such that the level of Impurity B remains not more than 0.3%, preferably below 0.2%, more preferably below 0.07% after storage at 40 degree Celsius and 75% RH for 6 months.

[0181] In some embodiments, the stability achieved by the composition may be such that the level of Impurity C remains not more than 0.3%, preferably below 0.2%, more preferably below 0.11% after storage at 25 degree Celsius and 60% RH for 24 months, or 29 months. In some embodiments, the stability achieved by the composition may be such that the level of Impurity C remains not more than 0.3%, preferably below 0.26%, more preferably below 0.25% after storage at 40 degree Celsius and 75% RH for 6 months.

[0182] In some embodiments, the stability achieved by the composition may be such that the level of Impurity D remains not more than 0.2%, preferably below 0.1%, more preferably below 0.05% after storage at 25 degree Celsius and 60% RH for 24 months, or 29 months. In some embodiments, the stability achieved by the composition may be such that the level of Impurity D remains below 0.3%, preferably below 0.2%, more preferably below 0.18% after storage at 40 degree Celsius and 75% RH for 6 months.

[0183] In some embodiments, the stability achieved by the composition may be such that the level of Impurity F remains below 0.3%, preferably below 0.11%, more preferably below

0.05% after storage at 25 degree Celsius and 60% RH for 24 months, or 29 months. In some embodiments, the stability achieved by the composition may be such that the level of Impurity F remains below 0.3%, preferably below 0.11%, more preferably below 0.05% after storage at 40 degree Celsius and 75% RH for 6 months.

[0184] In some embodiments, the stability achieved by the composition may be such that the level of Impurity G remains below 0.3%, preferably below 0.11%, more preferably below 0.05% after storage at 25 degree Celsius and 60% RH for 24 months, or 29 months. In some embodiments, the stability achieved by the composition may be such that the level of Impurity G remains below 0.3%, preferably below 0.11%, more preferably below 0.05% after storage at 40 degree Celsius and 75% RH for 6 months.

[0185] In some embodiments, the stability achieved by the composition may be such that the level of the Sulphite Adduct remains below 0.21%, preferably below 0.1%, more preferably below 0.05% after storage at 25 degree Celsius and 60% RH for 24 months, or 29 months. In some embodiments, the stability achieved by the composition may be such that the level of Sulphite Adduct remains below 0.21%, preferably below 0.1%, more preferably below 0.05% after storage at 40 degree Celsius and 75% RH for 6 months.

[0186] In some embodiments, the stability achieved by the composition may be such that the level of the Unspecified Impurity remains below 0.21%, preferably below 0.17%, more preferably below 0.14% after storage at 25 degree Celsius and 60% RH for 24 months, or 29 months. In some embodiments, the stability achieved by the composition may be such that the level of the Unspecified Impurity remains below 0.21%, preferably below 0.16%, more preferably below 0.11% after storage at 40 degree Celsius and 75% RH for 6 months.

[0187] In some embodiments, the stability achieved by the composition may be such that the level of the Total Impurities remains below 2.9%, preferably below 1%, more preferably below 0.6% after storage at 25 degree Celsius and 60% RH for 24 months, or 29 months. In some embodiments, the stability achieved by the composition may be such that the level of the Total Impurities remains below 2.9%, preferably below 2%, more preferably below 1.7% after storage at 40 degree Celsius and 75% RH for 6 months.

[0188] In some embodiments, the stability achieved by the composition may be such that the level of the pH remains within a range of 7.4 – 7.8, preferably within a range of 7.5 – 7.7 after storage at 25 degree Celsius and 60% RH for 24 months, or 29 months. In some embodiments, the stability achieved by the composition may be such that the level of the pH remains within a range of 7.4 – 7.8, preferably within a range of 7.5 – 7.7 after storage at 40 degree Celsius and 75% RH for 6 months.

[0189] In some embodiments, where sodium sulfite is the antioxidant preservative, the concentration is between 0 – 70 ppm Sodium Sulfite (Anhydrous). In a specific embodiment of the invention, the formulation referred to as Formulation 10 (F10) containing 0 mg/ml Sodium Sulfite Anhydrous, 5.1% headspace Oxygen, and about 6 to 9 ml headspace volume showed an stable assay profile (for 29 months with a projection out to 48 months) in terms of Dexamethasone Phosphate equivalent content between about 906 and 1306 mg, and an acceptable impurity profile even in the absence of any sodium sulfite.

[0190] The present disclosure is directed to glucocorticoid containing pharmaceutical compositions having reduced levels of antioxidants. The ability to reduce the levels of antioxidants, which leads to a reduction in the toxic side effects associated with the use of such antioxidants, is a result of decreasing the headspace volume to total API ratio beyond what is typically used in the industry (Table 1). Accordingly, in a specific aspect of the invention, the ratio of headspace volume [ml] to total API (Dexamethasone Phosphate equivalent) [mg] ratio is between 0 to about 0.00588. In a preferred embodiment, the "(Sulfite:API) x headspace volume" - value is between 0 to about 0.05. In the most preferred embodiment, the "(Sulfite:API) x headspace volume" – value is between 0 to about 0.02.

[0191] At an accelerated storage condition of 40°C (75% relative humidity-RH) elimination of Disodium Edetate at two different headspace oxygen levels (0%, 5%,), with headspace volume between about 6-9 ml still maintains stability out to about 12 months (measured for 6 months with a projection out to 12 months) with the reduced headspace volume to API ratio of between about 0.0046 to about 0.0099. The latter constitutes a formulation made solely of GRAS excipients. Elimination of both Sodium Sulfite (Anhydrous) and Disodium Edetate is also possible with maintained stability out to 3 months with a headspace volume to API ratio of between about 0.0046 to about 0.0099 at an accelerated storage condition (40°C/75%RH). The result of F10 (at 25°C/60%RH) demonstrates that a shelf-life of at least 29 months or

longer can be achieved without any antioxidants present. Moreover, at ICH-defined accelerated storage condition of 40°C/75% RH (tested up to 6 months), while lacking Disodium Edetate, increasing concentrations of Dexamethasone Sodium Phosphate (10 - 40 mg/ml or 10 – 200 mg/ml) lead to a decrease in total impurities. The ability to employ reduced levels of antioxidants, as disclosed in detail herein, results from a decrease in the headspace volume to API ratio when the compositions are distributed into packaging receptacles as well as due to the finding that Dexamethasone Sodium Phosphate becomes increasingly self-protective (against degradation) in higher concentration in a solution.

* * *

[0192] The present disclosure is also directed to use of the pharmaceutical compositions disclosed herein for treatment of patients in need of glucocorticoid drugs. Such treatment includes administration of the compositions to patients in need of anti-inflammatory, immunosuppression, lymphoablation, germinal center elimination, IL-2, IL-7, IL-12 and/or IL-15 elevation, mesenchymal stem cell elevation, G-CSF increase, neutrophil increase, tumor/cancer killing or lymphodepletion (preconditioning) before cell- based therapy, for example.

[0193] Accordingly, the present invention also provides the aqueous pharmaceutical formulations as disclosed herein for use in a method of treatment.

[0194] The present invention also provides the use of the aqueous pharmaceutical formulations as disclosed herein for the preparation of a medicament for use in a method of treatment.

[0195] The present invention also provides a method of treatment comprising administering to a subject in need thereof, a therapeutically effective amount of the aqueous pharmaceutical formulations as disclosed herein.

[0196] In some embodiments, the method is a method of reducing stem cell accumulation in the spleen in a subject, the method comprising administering the formulation to the subject prior to stem cell treatment. Such methods are disclosed, for example, in WO 2012/024519. In some embodiments, the method is a method of enhancing adoptive cellular therapy (ACT) in a subject, the method comprising administering the formulation to the subject prior to adoptive cellular therapy. Such methods are disclosed, for example, in WO 2018/183927. In

some embodiments the method is a method of treatment of a lymphocyte mediated disease in a subject, the method comprising administering the formulation to the subject. Such methods are disclosed, for example, in PCT/US2019/054395.

[0197] As used herein, “patient in need thereof” and “subject in need thereof” may include individuals, e.g., mammals such as humans, canines, felines, porcines, etc., that have been diagnosed with inflammatory, immunosuppressive or cancer disorders. "Treating", "treatment" or “treat” can refer to the following: alleviating or delaying the appearance of clinical symptoms of a disease or condition in a patient that may be afflicted with or predisposed to the disease or condition, but does not yet experience or display clinical or subclinical symptoms of the disease or condition.

[0198] In certain embodiments, “treating”, “treat” or “treatment” may refer to preventing the appearance of clinical symptoms of a disease or condition in a patient that may be afflicted with or predisposed to the disease or condition, but does not yet experience or display clinical or subclinical symptoms of the disease or condition. "Treating", “treat” or "treatment" also refers to inhibiting the disease or condition, *e.g.*, arresting or reducing its development or at least one clinical or subclinical symptom thereof. "Treating", “treat” or "treatment" further refers to relieving the disease or condition, *e.g.*, causing regression of the disease or condition or at least one of its clinical or subclinical symptoms. The benefit to a patient to be treated may be statistically significant, mathematically significant, or at least perceptible to the patient and/or the physician. Nonetheless, prophylactic (preventive) treatment and therapeutic (curative) treatment are two separate embodiments of the disclosure herein.

[0199] Other uses of the compositions include use of a stem cell preparation and a therapeutic agent that inhibits binding of the stem cells to germinal centers within lymphoid tissue, in the manufacture of a medicament for regenerating a damaged tissue or organ in a subject who does not require hematological recovery due to cancer therapy, non-myeloablative therapy or myeloablative therapy, including chemotherapy, radiation, and combination treatments, wherein the therapeutic agent does not block the binding of the stem cells to damaged organ or tissue, thereby augmenting the numbers of circulating stem cells that can be attracted to target tissue or organ to regenerate the damaged organ or tissue.

[0200] Administering" refers to the physical introduction of an agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. Exemplary routes of administration for the formulations disclosed herein include intravenous, intramuscular, subcutaneous, intraperitoneal, spinal or other parenteral routes of administration, for example by injection or infusion. The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion, as well as in vivo electroporation. In some embodiments, the formulation is administered via a non-parenteral route, e.g., orally. Other non-parenteral routes include a topical, epidermal or mucosal route of administration, for example, intranasally, vaginally, rectally, sublingually or topically.

[0201] The term 'site of injection' as used herein non-exclusively relates to intra-tumor, or intra-organ such as the kidney or liver or pancreas or heart or lung or brain or spleen or eye, intra-muscular, intro-ocular, intra-striatal, intradermal, by dermal patch, by skin patch, by patch, into the cerebrospinal fluid, into the brain, among others.

* * *

[0202] The present disclosure is also related to methods for production of high concentration glucocorticoid containing pharmaceutical compositions comprising reduced levels of antioxidant preservatives. Such methods comprise the step of mixing the components of the composition and packaging said composition in an environment wherein the headspace volume to API ratio is decreased.

[0203] In a specific aspect of the invention, the headspace volume to API ratio is 0-0.00588. In such instances, the utilization of such a ratio during packaging permits one to use decreased concentrations of preservatives, such as for example, decreased levels of sulfites. In one aspect, the concentration of a sulfite is 0 – 70 ppm. For packaging, the headspace volume can be measured by calculation (vial brim volume – stopper volume – fluid fill volume) or by adding a liquid and measuring the volume when all gas has been replaced.

[0204] Also disclosed is a method for stabilising an aqueous pharmaceutical formulation comprising a glucocorticoid, the method comprising packaging an aqueous pharmaceutical formulation as disclosed herein into a container with a headspace volume (ml) to total glucocorticoid content (mg) ratio of 0.007 or less. In some preferred embodiments, the headspace volume (ml) to total glucocorticoid content (mg) ratio is 0.00588 or less.

[0205] Other embodiments of the present invention will be apparent to those skilled in the art from consideration of the present specification and practice of the present invention disclosed herein. It is intended that the present specification and examples be considered as exemplary only with a true scope and spirit of the invention being indicated by the following claims and equivalents thereof.

Definitions

[0206] As used herein, "maintaining the assay" means maintaining quantitative chemical attributes of a formulation within acceptable limits as compared to values at the time of manufacture. This can be deteremined, for example, by assaying quantitative chemical attributes of a formulation and comparing these with the same attributes measured at the time of manufacture. In specific cases this refers to assaying levels / amounts of the active pharmaceutical ingredient (API) in the formulation and comparing this to the level / amount at the time of manufacture. In other cases this may also refer to assaying levels / amounts of degradation products of the active pharmaceutical ingredient (API), or the levels / amounts of unknown impurities in the formulation. In other cases this may also refer to assaying levels / amounts of total impurities in the formulation.

[0207] The term "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; Band C; A (alone); B (alone); and C (alone).

[0208] The use of the alternative (e.g., "or") should be understood to mean either one, both, or any combination thereof of the alternatives. As used herein, the indefinite articles "a" or "an" should be understood to refer to "one or more" of any recited or enumerated component.

[0209] As described herein, any concentration range, percentage range, ratio range or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one-tenth and one-hundredth of an integer), unless otherwise indicated.

[0210] The term "about" when referring to a measurable value such as an amount or a temporal duration and the like refers to variations of +/- 20% or +/- 10% or +/- 5%. That is, the term “about” refers to a value or composition that is within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, i.e., the limitations of the measurement system. For example, "about" can mean within 1 or more than 1 standard deviation per the practice in the art. Alternatively, "about" can mean a range of up to 20% (i.e., ±20%). For example, about 3 mg can include any number between 2.3 mg and 3.6 mg (for 20%). Furthermore, particularly with respect to biological systems or processes, the terms can mean up to an order of magnitude or up to 5-fold of a value. When particular values or compositions are provided in the application and claims, unless otherwise stated, the meaning of"about" should be assumed to be within an acceptable error range for that particular value or composition such as one-tenth.

[0211] In the present disclosure concentrations may be expressed as e.g. grams per litre (g/l) or milligrams per milliliter (mg/ml). Concentrations may also be expressed as parts per million (ppm). One gram in 1000 ml (1 g/l) is equivalent to 1000 ppm. Thus, one milligram in 1000 ml (1 mg/l) is one ppm, and one milligram in 1 ml (1 mg/ml) is 1000 ppm. Similarly, 0.1 mg/ml is 100ppm, 0.07 mg/ml is 70 ppm, and 0.01 mg/ml is 10 ppm. Those skilled in the art can readily convert between concentrations expressed in mg/ml and ppm.

[0212] The following examples are presented to further illustrate selected embodiments of the present invention.

EXAMPLES

EXAMPLE METHOD

[0213] Assay and Related Substances (UPLC) for Dexamethasone Phosphate Injection. Details of a UPLC method for the determination of dexamethasone phosphate and related substances in a pharmaceutical formulation.

Method Requirement	**Description**
Technique	Ultra Performance Liquid Chromatography (UPLC)
Reagents	WFI (Water for Injection) Ammonium Acetate, ACS reagent grade or equivalent Acetic Acid, ACS reagent Methanol, HPLC Grade or equivalent
UPLC System	Column: C8 Detector: UV Total Run Time: 10 minutes Elution Method: Gradient elution
Mobile phase	Mobile Phase A (Example Preparation) • Dissolve 3.5 g of ammonium acetate in 1000 mL of WFI. • Adjust the pH of the ammonium acetate buffer to 3.8 with glacial acetic acid. Mobile Phase B 100% Methanol
Diluent	Example Preparation Methanol and Mobile phase A, mixed thoroughly.
Standard	1mg/ml in Dexamethasone Phosphate in diluent
Sample preparation for assay and related substances	1mg/ml in Dexamethasone Phosphate in diluent

EXAMPLE 1

[0214] Table 1 shows a comparison of selected Dexamethasone Sodium Phosphate solutions (vials or ampouls) in the market to AVM0703 in terms of estimated/measured headspace volume, API concentration and content, sulfite concentration and content as well as chosen, calculated ratios: AVM0703 is below the values typically found in manufactured Dexamethasone Sodium Phosphate formulations in the industry concerning headspace volume [ml] to total API (Dexamethasone Phosphate equivalent) [mg] ratio, total Sulfite [mg] to total API (Dexamethasone Phosphate equivalent) [mg] ratio as well as one of the lowest regarding the "(Sulfite/API) x Headspace Volume" value.

Table 1

Company name	Product name	NDC (or foreign drug code)	Estimated headspace (ml)	API conc. (as DP in mg/ml)	Vial (or Ampoule) volume (ml)	Total API (as DP in mg)	Sulfite conc. (mg/ml)	Total sulfite (mg)	Real headspace (liquid injected, vol. measured) (ml)
AVM Biotechnology	AVM0703		8.00	24	51	1224	0.035	1.785	7.2
Hameln pharmaceuticals	Dexamethasone	01502/0079	0.75	10	10	100			
Merck	Decadron, withdrawn	0006-7646-03	0.90	24	5	120	1	5	
Hospira	DBL™ (Dexamethasone Sodium Phosphate)	n/a	0.90	24	5	120			
Fuji Pharma (Japan)	Solcort	22000AMX 00346000	0.90	24	5	120			
Physicians Total Care, Inc.	Dexamethasone Sodium Phosphate	54868-6099-0	1.92	10	10	100	1	10	
West-Ward Pharmaceuticals Corp.	Dexamethasone Sodium Phosphate	0641-0367-25	0.20	10	1	10	1.5	1.5	
Mylan	Dexamethasone Sodium Phosphate	67457-420-00	1.92	10	10	100			2
Fresenius (pres. free)	Dexamethasone Sodium Phosphate	63323-506-01	0.20	10	1	10			
West-Ward Pharmaceuticals Corp.	Dexamethasone Sodium Phosphate	0641-6146-01	0.75	4	5	20	1	5	
Fresenius (preserved)	Dexamethasone Sodium Phosphate	63323-516-10	3.64	10	10	100			4.04
Henry Schein Animal Health	Dexaject SP*	11695-4013-1	18.00	3.66	100	366	2	200	
Hospira	Dexamethasone	04515/0019	0.40	4	2	8	0.07	0.14	
* all products for human use except Dexaject SP (horse)									

Table 1 (continued)

Company name	Product name	Headspace volume (ml) to total API (as DP in mg) ratio	Sulfite (mg) to total API (as DP in mg) ratio	Sulfite : API : Headspace ratio	(Sulfite : API) x Headspace value
AVM Biotechnology	AVM0703	0.00588	0.00146	0.000203	0.01050
Hameln pharmaceuticals	Dexamethasone	0.00750			
Merck	Decadron, withdrawn	0.00750	0.04167	0.046296	0.03750
Hospira	DBL™ (Dexamethasone Sodium Phosphate)	0.00750			
Fuji Pharma (Japan)	Solcort	0.00750			
Physicians Total Care, Inc.	Dexamethasone Sodium Phosphate	0.01920	0.10000	0.052083	0.19200
West-Ward Pharmaceuticals Corp.	Dexamethasone Sodium Phosphate	0.02000	0.15000	0.750000	0.03000
Mylan	Dexamethasone Sodium Phosphate	0.0200			
Fresenius (pres. free)	Dexamethasone Sodium Phosphate	0.0200			
West-Ward Pharmaceuticals Corp.	Dexamethasone Sodium Phosphate	0.03750	0.25000	0.333333	0.18750
Fresenius (preserved)	Dexamethasone Sodium Phosphate	0.04040			
Henry Schein Animal Health	Dexaject SP*	0.04918	0.54645	0.030358	9.83607
Hospira	Dexamethasone	0.05000	0.01750	0.043750	0.00700
* all products for human use except Dexaject SP (horse)					

EXAMPLE 2

[0215] Composition of the Target Point Formulation of the DoE experiment in mg/ml.

Table 2 – AVM0703 Target Point Formulation, Design of Experiment

Component	Amount / value	
Dexamethasone Phosphate	24 mg	Equivalent to Dexamethasone Sodium Phosphate: 26.23 mg; Equivalent to Dexamethasone: 19.94 mg
Sodium Citrate	10 mg	GRAS excipient
Disodium EDTA	0.5 mg	
Sodium Sulfite Anhydrous	0.035 mg	GRAS excipient
Water for injection	q.s. to 1.00 ml	
pH (NaOH/HCl 0.1/1N)	7.6	
Oxygen headspace	5%	

[0216] Composition of the Target Point (center point) Formulation of the DoE experiment in weight percent (concentration).

Table 3

Component	Concentration (%)	Type
Dexamethasone Sodium Phosphate	2.53	Active
Sodium Citrate	0.96	Buffer
Disodium Edetate	0.048	Chelator
Sodium Sulfite (Anhydrous)	0.0034	Antioxidant
Water for injection	96.45	Solvent

[0217] Design of Experiment study formulations: 10 of the 16 formulations were monitored for long-term storage (25°C/60%RH). As part of the Design of Experiment study that was monitored for 29 months at 25°C/60% RH, 16 formulations were prepared. Table 4 shows specifications / composition of 10 out of the 16 formulations. Formulation 14 experienced atmospheric exposure by accident and was not used for the study. All formulations were described as clear, yellowish solutions. All formulations contained 26.23 mg/ml DSP, which is equivalent to 24 mg/ml dexamethasone phosphate (DP) as well as 0.05 mg/ml Disodium EDTA and 10 mg/ml Sodium Citrate. All formulations were packaged using the AVM0703 headspace volume (ml) to dexamethasone content (mg) ratio outlined in Table 1 (24 mg/ml dexamethasone phosphate; 51 ml vial; 7.2 ml headspace volume; headspace volume (ml) to dexamethasone content (mg) ratio of about 0.00588).

Table 4

Formulation No.	DSP (mg/ml)	Sodium Citrate (mg/ml)	Disodium Edetate (mg/ml)	Sodium Sulfite (mg/ml)	Headspace Oxygen (%), set point	Headspace Oxygen (%), actual
2	26.23	10	0.5	0.035	5.00	5.4
4				0.035	5.00	5.4
6				0.035	5.00	5.2
8				0.035	5.00	5.1
9				0.070	5.00	5.1
10				0.000	5.00	5.1
11				0.035	10.00	10.4
12				0.035	5.00	5.1
15				0.035	20.90	n/a
16				0.070	20.90	n/a

[0218] AVM0703 – Design of Experiment – six formulations were monitored for over 18 months (25°C/ 60% RH). Six formulations with varying levels of Sodium Sulfite (Anhydrous) and Headspace Oxygen which were tested for stability at 18 months. Aside from F15 (atmospheric Oxygen level of 20.9%), all 5 other formulations (F2, 4, 9, 10 and 11) were within the required API assay or impurity thresholds. Those six were selected from 15 formulations that were manufactured for the DoE study to assess those 2 factors: 13 formulations (F1 – F13) to assess Sodium Sulfite (Anhydrous) in a range of 0 to 0.07 mg/mL and Headspace Oxygen in a range of 0 to 10%, while 2 additional formulations (F15, F16) were manufactured to assess stability at atmospheric Oxygen (20.9%) using 0.035 or 0.07 mg/ml, respectively. Results are shown in Table 5.

Table 5 – 18 months stability

	Target point			No sulfite		
Formulation #	**2**	**4**	**9**	**10**	**11**	**15**
Assay % (95.0 – 105.0 %)	98.5	98.4	98.3	98.6	98.1	97.9
Impurity A (%) (NMT 0.5%)	0.20	0.20	0.20	0.20	0.20	0.40
Impurity B (%) (NMT 0.5%)	0.10	0.10	0.10	0.10	0.10	0.10
Impurity C (%) (NMT 0.5%)	0.10	0.10	0.10	0.10	0.10	0.10
Impurity D (%) (NMT 0.5%)	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Impurity F (%) (NMT 0.5%)	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Impurity G (%) (NMT 0.5%)	<0.05	<0.05	<0.05	0.10	0.10	0.10

Sulphite adduct (NMT 0.2%)	*n/a	*n/a	*n/a	*n/a	*n/a	*n/a
Any unspecified impurity (%) (NMT 0.2%)	0.17	0.16	0.17	0.15	0.17	0.37
Total impurities (%) (NMT 3.0%)	0.4	0.4	0.5	0.4	0.5	1.0
pH (7.4-7.8)	7.6	7.7	7.7	7.6	7.6	7.5
Sodium Sulfite (mg/ml)	0.035	0.035	0.070	0.000	0.035	0.035
Headspace Oxygen (%), set point	5.00	5.00	5.00	5.00	10.00	20.90
Headspace Oxygen (%), actual	5.4	5.4	5.1	5.1	10.4	n/a

NMT = not more than (threshold)

[0219] AVM0703 – Design of Experiment – nine formulations were monitored for over 24 months (25°C/ 60% RH). Nine formulations with varying levels of Sodium Sulfite (Anhydrous) and Headspace Oxygen which were tested for stability at 24 months. Aside from F15 (atmospheric Oxygen level of 20.9%), all other 8 formulations (F2, 4, 6, 8, 9, 10, 11 and 12) were within the required API assay or impurity thresholds. Those nine were selected from 15 formulations that were manufactured for the DoE study to assess those 2 factors: 13 formulations (F1 – F13) to assess Sodium Sulfite (Anhydrous) in a range of 0 to 0.07 mg/mL and Headspace Oxygen in a range of 0 to 10%, while 2 additional formulations (F15, F16) were manufactured to assess stability at atmospheric Oxygen (20.9%) using 0.035 or 0.07 mg/ml, respectively. Results are shown in Table 6.

Table 6 – 24 months stability

	Target point (TP)					No sulfite		TP	
Formulation #	**2**	**4**	**6**	**8**	**9**	**10**	**11**	**12**	**15**
Assay % (95.0 – 105.0 %)	97.4	97.2	96.7	96.8	95.7	96.9	96.7	98.1	96.7
Impurity A (%) (NMT 0.5%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.5
Impurity B (%) (NMT 0.5%)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Impurity C (%) (NMT 0.5%)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Impurity D (%) (NMT 0.5%)	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.1
Impurity F (%) (NMT 0.5%)	<0.05	0.1	0.1	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

Impurity G (%) (NMT 0.5%)	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.10	<0.05	0.10
Sulphite adduct (NMT 0.2%)	*n/a	*n/a	*n/a	*n/a	*n/a	*n/a	*n/a	*n/a	*n/a
Any unspecified impurity (%) (NMT 0.2%)	0.13	0.16	0.13	0.14	0.13	0.15	0.16	0.13	0.41
Total impurities (%) (NMT 3.0%)	0.5	0.5	0.5	0.5	0.5	0.5	0.6	0.5	1.2
pH (7.4-7.8)	7.7	7.7	7.7	7.6	7.7	7.7	7.6	7.6	7.5
Sodium Sulfite (mg/ml)	0.035	0.035	0.035	0.035	0.070	0.000	0.035	0.035	0.035
Headspace Oxygen (%), set point	5.00	5.00	5.00	5.00	5.00	5.00	10.00	5.00	20.90
Headspace Oxygen (%), actual	5.4	5.4	5.2	5.1	5.1	5.1	10.4	5.1	n/a

NMT = not more than (threshold)

[0220] AVM0703 – Design of Experiment – nine formulations were monitored for over 29 months (25°C/ 60% RH). Nine formulations with varying levels of Sodium Sulfite (Anhydrous) and Headspace Oxygen which were tested for stability at 29 months. Aside from F15 (atmospheric Oxygen level of 20.9%), all other 8 formulations (F2, 4, 6, 8, 9, 10, 11 and 12) were within the required API assay or impurity thresholds. Those nine were selected from 15 formulations that were manufactured for the DoE study to assess those 2 factors: 13 formulations (F1 – F13) to assess Sodium Sulfite (Anhydrous) in a range of 0 to 0.07 mg/mL and Headspace Oxygen in a range of 0 to 10%, while 2 additional formulations (F15, F16) were manufactured to assess stability at atmospheric Oxygen (20.9%) using 0.035 or 0.07 mg/ml Sodium Sulfite (Anhydrous), respectively. Results are shown in Table 7.

Table 7 – 29 months stability

	Target point (TP)					No sulfite		TP	
Formulation #	**2**	**4**	**6**	**8**	**9**	**10**	**11**	**12**	**15**
Assay % (95.0 – 105.0 %)	98.3	98.2	97.9	97.5	97.0	98.1	98.3	99.0	97.7
Impurity A (%) (NMT 0.5%)	0.3	0.2	0.3	0.3	0.2	0.3	0.3	0.3	0.6
Impurity B (%) (NMT 0.5%)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Impurity C (%) (NMT 0.5%)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Impurity D (%) (NMT 0.5%)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Impurity F (%) (NMT 0.5%)	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Impurity G (%) (NMT 0.5%)	<0.05	<0.05	<0.05	<0.05	<0.05	0.10	<0.05	<0.05	0.10
Sulphite adduct (NMT 0.2%)	*n/a	*n/a	*n/a	*n/a	*n/a	*n/a	*n/a	*n/a	*n/a
Any unspecified impurity (%) (NMT 0.2%)	0.20	0.20	0.19	0.20	0.19	0.19	0.19	0.20	0.48
Total impurities (%) (NMT 3.0%)	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	1.4
pH (7.4-7.8)	7.6	7.7	7.6	7.6	7.7	7.6	7.6	7.6	7.5
Sodium Sulfite (mg/ml)	0.035	0.035	0.035	0.035	0.070	0.000	0.035	0.035	0.035
Headspace Oxygen (%), set point	5.00	5.00	5.00	5.00	5.00	5.00	10.00	5.00	20.90
Headspace Oxygen (%), actual	5.4	5.4	5.2	5.1	5.1	5.1	10.4	5.1	n/a

NMT = not more than (threshold)

[0221] Design of experiment result for 29 months for the active pharmaceutical ingredient API in the AVM0703 formulation. (FIG. 1) Dexamethasone Sodium Phosphate (DSP). Six formulations with varying levels of Sodium Sulfite (Anhydrous) and Headspace Oxygen are tested for stability. Formulation 2 and 4 (F2, 4) are target point formulations with 0.035 mg/ml Sodium Sulfite (Anhydrous) and 5% Headspace Oxygen (95% nitrogen). The result demonstrates that the formulations are within a range of 95-105% DSP content for the tested values of Sodium Sulfite (Anhydrous) of 0 (F10), 0.035 (F2, 4, 11, 15) and 0.07 mg/ml (F9) at 5% (F2, 4, 9, 10), 10% (F11) and 20.90% (F15) headspace oxygen, not dropping below 95% for any formulation tested (25°C/ 60%RH).

[0222] Design of experiment result for 29 months for the "Impurity A" (free Dexamethasone) in the AVM0703 formulation. (FIG. 2) The result demonstrates that all the tested formulations are within a range of NMT (not more than) 1% (initially 0.5%, then increased to 1%) for free Dexamethasone (Imp A). Tested values of Sodium Sulfite (Anhydrous) were 0 (F10), 0.035 (F2, 4, 11, 15) and 0.07 mg/ml (F9) at 5% (F2, 4, 9, 10), 10% (F11) and 20.90% (F15) headspace oxygen. Free Dexamethasone accumulates due to acid hydrolysis from DSP (25°C/ 60%RH).

[0223] Design of experiment result for 29 months for "Any Unspecified Impurity" in the AVM0703 formulation. (FIG. 3) The result demonstrates that all the tested formulations are within a range of NMT (not more than) 0.2% for not yet identified impurities. Tested values of Sodium Sulfite (Anhydrous) were 0 (F10), 0.035 (F2, 4, 11, 15) and 0.07 mg/ml (F9) at 5% (F2, 4, 9, 10), 10% (F11) and 20.90% (F15) headspace oxygen. Only formulation F15 (at atmospheric oxygen level) was above the threshold for the last time point (25°C/ 60%RH).

[0224] Design of experiment result for 29 months for the "Total Impurity" in the AVM0703 formulation. (FIG. 4). The result demonstrates that all the tested formulations are within a range of NMT (not more than) 3%. Tested values of Sodium Sulfite (Anhydrous) were 0 (F10), 0.035 (F2, 4, 11, 15) and 0.07 mg/ml (F9) at 5% (F2, 4, 9, 10), 10% (F11) and 20.90% (F15) headspace oxygen (25°C/ 60%RH).

[0225] Fig. 5: Design of Experiment target point formulations 2 and 4 (F2, F4): 0.035 mg/ml Sodium Sulfite Anhydrous, 5.4% headspace oxygen. The projection with 6 measured (up to 29 months) data points shows for both formulations that the Dexamethasone Sodium Phosphate content is expected to be above 95% for 48 months (25°C/ 60%RH).

[0226] Fig. 6: Design of Experiment formulation 9 (F9): 0.07 mg/ml Sodium Sulfite Anhydrous, 5.1% headspace oxygen. The projection with 6 measured (up to 29 months) data points shows for the formulation that the Dexamethasone Sodium Phosphate content is expected to be above 95% for 48 months (25°C/ 60%RH).

[0227] Fig. 7: Design of Experiment formulation 10 (F10): 0 mg/ml Sodium Sulfite Anhydrous, 5.1% headspace oxygen. The projection with 6 measured data points (up to 29 months) shows for the formulation that the Dexamethasone Sodium Phosphate content is expected to be above 95% for 48 months (25°C/ 60%RH).

[0228] Fig. 8: Design of Experiment formulation 11 (F11): 0.035 mg/ml Sodium Sulfite Anhydrous, 10.4% headspace oxygen. The projection with 6 measured data points (up to 29 months) shows for the formulation that the Dexamethasone Sodium Phosphate content is expected to be above 95% for 36 months (25°C/ 60%RH).

[0229] Fig. 9: Design of Experiment formulation 15 (F15): 0.035 mg/ml Sodium Sulfite Anhydrous, 20.9% headspace oxygen. The projection with 6 measured data points (up to 29 months) shows for the formulation that the Dexamethasone Sodium Phosphate content is expected to be above 95% for 48 months (25°C/ 60%RH).

[0230] Fig. 10: Design of Experiment target point formulations 2 and 4 (F2, F4): 0.035 mg/ml Sodium Sulfite Anhydrous, 5.4% headspace oxygen. The projection with 6 measured data points (up to 29 months) shows for both formulations that the Impurity A is expected to be below 0.5% for 48 months (25°C/ 60%RH).

[0231] Fig. 11: Design of Experiment formulation 9 (F9): 0.07 mg/ml Sodium Sulfite Anhydrous, 5.1% headspace oxygen. The projection with 6 measured data points (up to 29 months) shows for the formulation that the Impurity A is expected to be below 0.5% for 48 months (25°C/ 60%RH).

[0232] Fig. 12: Design of Experiment formulation 10 (F10): 0 mg/ml Sodium Sulfite Anhydrous, 5.1% headspace oxygen. The projection with 6 measured data points (up to 29 months) shows for the formulation that the Impurity A is expected to be below 0.5% for 48 months (25°C/ 60%RH).

[0233] Fig. 13: Design of Experiment formulation 11 (F11): 0.035 mg/ml Sodium Sulfite Anhydrous, 10.4% headspace oxygen. The projection with 6 measured data points (up to 29 months) shows for the formulation that the Impurity A is expected to be below 0.5% for 48 months (25°C/ 60%RH).

[0234] Fig. 14: Design of Experiment formulation 15 (F15): 0.035 mg/ml Sodium Sulfite Anhydrous, 20.9% headspace oxygen (atmospheric). The projection with 6 measured data points (up to 29 months) shows for the formulation that the Impurity A crossed 0.5% at 24 months, while the projection shows for this impurity to be expected less than 1% for 48 months (25°C/ 60%RH).

[0235] Fig. 15: Design of Experiment formulation 2 (F2): 0.035 mg/ml Sodium Sulfite Anhydrous, 5.4% headspace oxygen. The projection with 6 measured data points (up to 29

months) shows for the formulation that the Unspecified Impurity reached 0.2% at 29 months, but is expected to be below 0.5% for 48 months (25°C/ 60%RH).

[0236] Fig. 16: Design of Experiment formulation 4 (F4): 0.035 mg/ml Sodium Sulfite Anhydrous, 5.4% headspace oxygen. The projection with 6 measured data points shows for the formulation that the Unspecified Impurity has reached 0.2% at 29 months, but is expected to be below 0.5% for 48 months (25°C/ 60%RH).

[0237] Fig. 17: Design of Experiment formulation 9 (F9): 0.070 mg/ml Sodium Sulfite Anhydrous, 5.1% headspace oxygen. The projection with 6 measured data points shows for the formulation that the Unspecified Impurity is expected to cross 0.2% at about 32 months, but to be below 0.5% for 48 months (25°C/ 60%RH).

[0238] Fig. 18: Design of Experiment formulation 10 (F10): 0 mg/ml Sodium Sulfite Anhydrous, 5.1% headspace oxygen. The projection with 6 measured data points shows for the formulation that the Unspecified Impurity is expected to cross 0.2% at 32months, but to be below 0.5% for 48 months (25°C/ 60%RH).

[0239] Fig. 19: Design of Experiment formulation 11 (F11): 0.035 mg/ml Sodium Sulfite Anhydrous, 10.4% headspace oxygen. The projection with 6 measured data points shows for the formulation that the Unspecified Impurity is expected to cross 0.2% at about 31 months, but to be below 0.5% for 48 months (25°C/ 60%RH).

[0240] Fig. 20: Design of Experiment formulation 15 (F15): 0.035 mg/ml Sodium Sulfite Anhydrous, 20.9% headspace oxygen (atmospheric). The 6 measured data points shows for the formulation that the Unspecified Impurity crossed 0.2% at about 10 months, and is expected to cross 0.5% at about 30 months (25°C/ 60%RH).

[0241] Fig. 21: Design of Experiment formulation 2 (F2): 0.035 mg/ml Sodium Sulfite Anhydrous, 5.4% headspace oxygen. The projection with 6 measured data points shows for the formulation that Total Impurities are expected to be below 3% for 48 months (25°C/ 60%RH).

[0242] Fig. 22: Design of Experiment formulation 4 (F4): 0.035 mg/ml Sodium Sulfite Anhydrous, 5.4% headspace oxygen. The projection with 6 measured data points shows for the formulation that Total Impurities are expected to be below 3% for 48 months (25°C/ 60%RH).

[0243] Fig. 23: Design of Experiment formulation 9 (F9): 0.07 mg/ml Sodium Sulfite Anhydrous, 5.1% headspace oxygen. The projection with 6 measured data points shows for the formulation that Total Impurities are expected to be below 3% for 48 months (25°C/ 60%RH).

[0244] Fig. 24: Design of Experiment formulation 10 (F10): 0 mg/ml Sodium Sulfite Anhydrous, 5.1% headspace oxygen. The projection with 6 measured data points shows for the formulation that Total Impurities are expected to be below 3% for 48 months (25°C/ 60%RH).

[0245] Fig. 25: Design of Experiment formulation 11 (F11): 0.035 mg/ml Sodium Sulfite Anhydrous, 10.4% headspace oxygen. The projection with 6 measured data points shows for the formulation that Total Impurities are expected to be below 3% for 48 months (25°C/ 60%RH).

[0246] Fig. 26: Design of Experiment formulation 15 (F15): 0.035 mg/ml Sodium Sulfite Anhydrous, 20.9% headspace oxygen (atmospheric). The projection with 6 measured data points shows for the formulation that Total Impurities are expected to be below 3% for 48 months (25°C/ 60%RH).

EXAMPLE 3

[0247] Extended DoE – Stability of formulations without Sodium Sulfite/Disodium Edetate. Design of experiment series (up to 6 months at 40°C/75%RH) to assess the stability of the formulation without the presence of either sodium sulfite or EDTA at increasing levels of headspace oxygen (0%, 5%, 10% and 15%): Ten formulations with the specifications shown in Table 8 were manufactured (GLP grade) and tested for stability. 26.23 mg/ml DSP equals 24 mg/ml Dexamethasone Phosphate. All formulations were packaged using the AVM0703 headspace volume (ml) to dexamethasone content (mg) ratio outlined in Table 1 (24 mg/ml dexamethasone phosphate; 51 ml vial; 7.2 ml headspace volume; headspace volume (ml) to dexamethasone content (mg) ratio of about 0.00588).

Table 8

Storage Condition	Batch	Formu-lation	Material				Headspace Oxygen (%)
			DSP (mg/ml)	Sodium Citrate (mg/ml)	Disodium Edetate (mg/ml)	Sodium Sulfite (Anhydrous) (mg/ml)	Target
40°C - Inverted	1	1	26.23*	10	0.50	0	0
40°C - Inverted	1	2					5
40°C - Inverted	1	3					10
40°C - Inverted	1	4					15
40°C - Inverted	2	1			0	0.035	0
40°C - Inverted	2	2					5
40°C - Inverted	2	3					10
40°C - Inverted	2	4					15
40°C - Inverted	3	1			0.50	0.035	0
40°C - Inverted	4	1			0	0	5

* Equivalent to 19.94 mg Dexamethasone and 24 mg Dexamethasone Phosphate

Table 9 – 1 month stability data (40°C/ 75%RH – inverted vial); All: Dexamethasone Phosphate 24 mg/ml, Sodium Citrate 10 mg/ml

Formulation #	1-1	1-2	1-3	1-4	2-1	2-2	2-3	2-4	3-1	4-1
Disodium EDTA (mg/ml)	0.5	0.5	0.5	0.5	0	0	0	0	0.5	0
Sodium Sulfite (mg/ml)	0	0	0	0	0.035	0.035	0.035	0.035	0.035	0
Headspace Oxygen (%)	0	5	10	15	0	5	10	15	0	5
Description	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
pH	7.7	7.7	7.6	7.6	7.8	7.8	7.8	7.7	7.7	7.7
Assay (%)	98.6	98.3	98.2	97.8	97.5	97.3	97.8	97.4	97.6	96.5
Impurity A (%) (NMT 1%)	0.15	0.13	0.11	0.11	0.13	0.13	0.13	0.13	0.17	0.12

Impurity B (%) (NMT 0.5%)	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
Impurity C (%) (NMT 0.5%)	0.1	0.1	0.09	0.09	0.11	0.11	0.1	0.1	0.1	0.1
Impurity D (%) (NMT 0.5%)	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Impurity F (%) (NMT 0.5%)	0.06	0.06	0.06	0.06	0.07	0.07	0.07	0.07	0.07	0.07
Impurity G (%) (NMT 0.5%)	0.16	0.18	0.19	0.19	0.15	0.19	0.2	0.21	0.15	0.18
Any unspecified impurity (%) (NMT 0.2%)	0.1	0.09	0.1	0.1	0.1	0.1	0.09	0.09	0.1	0.1
Total impurities (%) (NMT 3.0%)	0.6	0.7	0.7	0.7	0.6	0.7	0.7	0.7	0.7	0.7

[0248] Design of experiment (Extended DoE) result for 1 month, either lacking sodium sulfite or disodium edetate or both (Table 9). Ten (all: 24 mg/ml as Dexamethasone Phosphate equivalent which corresponds to 26.23 DSP mg/ml; 10 mg/ml sodium citrate) formulations with two different levels (0 or 0.035 mg/ml) of sodium sulfite (anhydrous), two different levels of disodium edetate (0 or 0.5 mg/ml) and four different levels of headspace oxygen (0, 5, 10, 15%) were tested for stability (40°C/75%RH). Formulations 1-1, 1-2, 1-3 and 1-4 lack sodium sulfite (anhydrous), contain 0.5 mg/ml disodium edetate and increasing amounts of headspace oxygen (1-1: 0%, 1-2: 5%, 1-3: 10%, 1-4: 15%). Formulations 2-1, 2-2, 2-3 and 2-4 lack disodium edetate, contain 0.035 mg/ml sodium sulfite (anhydrous) and increasing amounts of headspace oxygen (2-1: 0%, 2-2: 5%, 2-3: 10%, 2-4: 15%). Formulation 3-1 contains 0.035 mg/ml sodium sulfite (anhydrous) and 0.5 mg/ml disodium edetate, but lacks headspace oxygen. Formulation 4-1 lacks sodium sulfite (anhydrous) and disodium edetate and contains 5% headspace oxygen. The result demonstrates that all ten formulations are within a range of 95-105% for the DSP content as well as within the set thresholds for the known (A: not more than 1%; B, C, D, F and G: not more than 0.5%) and unknown impurities (not more than 0.2%), with 'Total Impurity' values far below the threshold of 3% (storage conditions are 40°C/75% RH, inverted).

[0249] Design of experiment (Extended DoE) result for 1, 3, and 6 months, either lacking sodium sulfite or disodium edetate or both (Figures 28-44). While all ten formulations passed the description at 3 months, only the following formulations passed the description as a clear solution at the 6 months stability time point: (batch#-formulation#) 2-1 (0.035 mg/ml

sodium sulfite, 0 mg/ml EDTA, 0% headspace oxygen), 2-2 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 5% headspace oxygen) and 3-1 (0.035 mg/ml sodium sulfite, 0.5 mg/ml EDTA, 0% headspace oxygen). All others showed precipitation at 6 months. Those three formulations (2-1, 2-2 and 3-1) were all within the acceptance criteria of the DSP assay (95-105%).

[0250] Fig. 28: Design of experiment result for the DSP assay (up to 6 months at 40°C/75%RH; 26.23 mg/ml DSP = 24 mg/ml DP) to assess the stability of the formulation without the presence of either sodium sulfite or EDTA at increasing levels of headspace oxygen (= HO: 0%, 5%, 10% and 15%): All ten formulations contained 26.23 mg/ml DSP, which is equivalent to 24 mg/ml Dexamethasone Phosphate (DP). While all ten formulations passed the description at 3 months, only the following formulations passed the description as a clear solution at the 6 months stability time point: (batch#-formulation#) 2-1 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 0% headspace oxygen), 2-2 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 5% headspace oxygen) and 3-1 (0.035 mg/ml sodium sulfite, 0.5 mg/ml EDTA, 0% headspace oxygen). All others showed precipitation at 6 months. The top chart shows the result of the DSP assay with the absolute values in percent, while the bottom chart depicts the difference in percent at 1, 3 and 6 months subtracted from the 0 months value (manufacture). The result shows that formulation 2-1 shows the least degradation of all formulations at the 6 months time point while still passing description (no precipitation).

[0251] Fig. 29 & 30: Design of experiment result for the impurities A and B (up to 6 months at 40°C/75%RH; 26.23 mg/ml DSP = 24 mg/ml DP): While all ten formulations passed the description at 3 months, only the following formulations passed the description as a clear solution at the 6 months stability time point: (batch#-formulation#) 2-1 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 0% headspace oxygen), 2-2 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 5% headspace oxygen) and 3-1 (0.035 mg/ml sodium sulfite, 0.5 mg/ml EDTA, 0% headspace oxygen). All others showed precipitation at 6 months. Fig. 29 shows the result of impurity A, while Fig. 30 depicts impurity B. The result shows that formulation 2-1 showed the lowest accumulation of impurity A (Dexamethasone) of all formulations at the 6 months time point. Impurity B was not increasing for any of the formulations.

[0252] Fig. 31 & 32: Design of experiment result for the impurites C and D (up to 6 months at 40°C/75%RH; 26.23 mg/ml DSP = 24 mg/ml DP): While all ten formulations passed the description at 3 months, only the following formulations passed the description as a clear

solution at the 6 months stability time point: (batch#-formulation#) 2-1 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 0% headspace oxygen), 2-2 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 5% headspace oxygen) and 3-1 (0.035 mg/ml sodium sulfite, 0.5 mg/ml EDTA, 0% headspace oxygen). All others showed precipitation at 6 months. Fig. 31 shows the result of impurity C, while Fig. 32 depicts impurity D. The result shows that the formulations with the highest headspace oxygen value showed the lowest accumulation of impurity C of all formulations at the 6 months time point. Impurity D increased the most from the 3 month time point to the 6 month time point for all formulations. Formulation 3-1 with sulfite and EDTA present at 0% headspace oxygen (HO) had the lowest value at 6 months of those 3 formulations that passed the description without a precipitate.

[0253] Fig. 33 & 34: Design of experiment result for the impurites F and G (up to 6 months at 40°C/75%RH; 26.23 mg/ml DSP = 24 mg/ml DP): While all ten formulations passed the description at 3 months, only the following formulations passed the description as a clear solution at the 6 months stability time point: (batch#-formulation#) 2-1 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 0% headspace oxygen), 2-2 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 5% headspace oxygen) and 3-1 (0.035 mg/ml sodium sulfite, 0.5 mg/ml EDTA, 0% headspace oxygen). All others showed precipitation at 6 months. Fig. 33 shows the result of impurity F, while Fig. 34 depicts impurity G. The result shows that none of the formulations increase for impurity F beyond the 0.2 % threshold. Regarding impurity G, formulation 2-1 showed the lowest accumulation of all formulations at the 6 months time point.

[0254] Fig. 35 & 36: Design of experiment result for the unidentified impurity with the highest value and the total impurities (up to 6 months at 40°C/75%RH; 26.23 mg/ml DSP = 24 mg/ml DP): While all ten formulations passed the description at 3 months, only the following formulations passed the description as a clear solution at the 6 months stability time point: (batch#-formulation#) 2-1 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 0% headspace oxygen), 2-2 (0.035 mg/ml sodium sulfite, 0 mg/ml EDTA, 5% headspace oxygen) and 3-1 (0.035 mg/ml sodium sulfite, 0.5 mg/ml EDTA, 0% headspace oxygen). All others showed precipitation at 6 months. Fig. 35 shows the result for the unidentified impurity with the highest value, while Fig. 36 depicts total impurities, which are the sum total of all previous impurities (A, B, C, D, F, G, highest unidentified impurity) as well as additionally all other unidentified impurities (with different retention times) that are of lower value. The result shows that the two sulfite formulations (of all three without precipitation at 6 months) lacking

EDTA (2-1, 2-2) show the lowest values of the highest unidentified impurity. Likewise, these same two formulations (2-1 and 2-2) are characterized by the lowest amount of total impurities. Therefore, for this formulation no EDTA is needed at a storage condition of 40°C/75%RH at 0 or 5% headspace oxygen.

[0255] Fig. 37: DSP result and projection of additional Design of Experiment formulations 2-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 0% Oxygen headspace), 2-2 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 5% headspace oxygen) and 3-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0.5 mg/ml EDTA and 0% headspace oxygen). The projection with 4 measured (up to 6 months) data points shows for the formulations that the Dexamethasone Sodium Phosphate content is expected to be at 95% for 12 months (40°C/ 75%RH) for the formulation 2-1, while 2-2 and 3-1 are expected to be at a level of about 93% and 93.5% respectively. The result shows that EDTA is not necessary to achieve a better stability for the formulation.

[0256] Fig. 38: Impurity A result and projection of additional Design of Experiment formulations 2-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 0% Oxygen headspace), 2-2 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 5% headspace oxygen) and 3-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0.5 mg/ml EDTA and 0% headspace oxygen). The projection with 4 measured (up to 6 months) data points shows for the formulations that the Impurity A level is expected to be below 1% for 12 months (40°C/ 75%RH) for the formulation 2-1 and 2-2, while for formulation 3-1 it is expected to reach 1% at about 9 months. The result shows that EDTA is not necessary to achieve a better stability for the formulation.

[0257] Fig. 39: Impurity C result and projection of additional Design of Experiment formulations 2-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 0% Oxygen headspace), 2-2 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 5% headspace oxygen) and 3-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0.5 mg/ml EDTA and 0% headspace oxygen). The projection with 4 measured (up to 6 months) data points shows for the formulations that the Impurity C level is expected to be at 0.5% for 12 months (40°C/ 75%RH) for the formulation 2-1, while being slightly below 0.5% for formulation 2-2 and 3-1 at this time point.

[0258] Fig. 40: Impurity D result and projection of additional Design of Experiment formulations 2-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 0% Oxygen headspace), 2-2 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 5% headspace oxygen) and 3-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0.5 mg/ml EDTA and 0% headspace oxygen). The projection with 4 measured (up to 6 months) data points shows that the Impurity D level is expected to be below 0.5% at 12 months (40°C/ 75%RH) for all 3 formulations.

[0259] Fig. 41: Impurity F result and projection of additional Design of Experiment formulations 2-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 0% Oxygen headspace), 2-2 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 5% headspace oxygen) and 3-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0.5 mg/ml EDTA and 0% headspace oxygen). The projection with 4 measured (up to 6 months) data points shows that the Impurity F level is expected to be below 0.5% at 12 months (40°C/ 75%RH) for all 3 formulations.

[0260] Fig. 42: Impurity G result and projection of additional Design of Experiment formulations 2-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 0% Oxygen headspace), 2-2 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 5% headspace oxygen) and 3-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0.5 mg/ml EDTA and 0% headspace oxygen). The projection with 4 measured (up to 6 months) data points shows that the Impurity G level is expected to be below 0.5% at 12 months (40°C/ 75%RH) for all 3 formulations.

[0261] Fig. 43: Unidentified Impurity result and projection of additional Design of Experiment formulations 2-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 0% Oxygen headspace), 2-2 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 5% headspace oxygen) and 3-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0.5 mg/ml EDTA and 0% headspace oxygen). The projection with 4 measured (up to 6 months) data points shows that the level of the Unidentified Impurity is expected to be below 0.5% at 12 months (40°C/ 75%RH) for all 3 formulations. Moreover, the two formulations lacking EDTA (2-1 and 2-2) show an expected level even below 0.2% at 12 months.

[0262] Fig. 44: Total Impurites result and projection of additional Design of Experiment formulations 2-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 0% Oxygen headspace), 2-2 (0.035 mg/ml Sodium Sulfite Anhydrous, 0 mg/ml EDTA and 5% headspace oxygen) and 3-1 (0.035 mg/ml Sodium Sulfite Anhydrous, 0.5 mg/ml EDTA and 0% headspace oxygen). The projection with 4 measured (up to 6 months) data points shows that the level of the Total Impurites is expected to be below 3% at 12 months (40°C/ 75%RH) for the two formulations lacking the EDTA (2-1, 2-2), while reaching 3% for the formulation 3-1 with sulfite and EDTA present. The result demonstrates that EDTA is not necessary to increase the stability of the formulation.

EXAMPLE 4

[0263] Six formulations with 3 varying levels of DSP (10, 30 and 45 mg/ml, equivalent to 9.15, 27.45 and 41.17 Dexamethsone Phosphate (DP)) with or without 0.5 mg/ml EDTA, respectively, were manufactured. The compositions of these six formulations is outlined in Tables 10 and 11. The formulations in Batch 1 and 2 (Table 10) were packaged with a headspace volume (ml) to dexamethasone content (mg) of 0.01543 (10 mg/ml dexamethasone sodium phosphate, equivalent to 9.15 mg/ml dexamethasone phosphate; 51 ml vial; 7.2 ml headspace volume; headspace volume (ml) to dexamethasone content (mg) ratio of about 0.01543). The formulations in Batch 3 and 4 (Table 10) were packaged with a headspace volume (ml) to dexamethasone content (mg) of 0.0514 (30 mg/ml dexamethasone sodium phosphate, equivalent to 27.45 mg/ml dexamethasone phosphate; 51 ml vial; 7.2 ml headspace volume; headspace volume (ml) to dexamethasone content (mg) ratio of about 0.00514). The formulations in Batch 1 and 2 (Table 11) were packaged with a headspace volume (ml) to dexamethasone content (mg) of 0.00343 (45 mg/ml dexamethasone sodium phosphate, equivalent to 41.17 mg/ml dexamethasone phosphate; 51 ml vial; 7.2 ml headspace volume; headspace volume (ml) to dexamethasone content (mg) ratio of about 0.00343).

Table 10

Storage Condition	**Batch**	**Material**				**Headspace Oxygen (%)**
		DSP (mg/ml)	**Sodium Citrate (mg/ml)**	**Disodium Edetate (mg/ml)**	**Sodium Sulfite (Anhydrous) (mg/ml)**	Target
40°C - Inverted	1	10	10	0.50	0	5

40°C - Inverted	2			0		
40°C - Inverted	3	30		0.50		
40°C - Inverted	4			0		

Table 11

Storage Condition	Batch	Material				Headspace Oxygen (%)
		DSP (mg/ml)	Sodium Citrate (mg/ml)	Disodium Edetate (mg/ml)	Sodium Sulfite (Anhydrous) (mg/ml)	Target
40°C - Inverted	1	45*	10	0.50	0	5
40°C - Inverted	2			0		

* Equivalent to 34.20 mg Dexamethasone and 41.17 mg Dexamethasone Phosphate

[0264] Results of the additional design of experiment for increasing concentrations of Dexamethasone Sodium Phosphate (DSP). Six formulations with 3 varying levels of DSP (10, 30 and 45 mg/ml, equivalent to 9.15, 27.45 and 41.17 Dexamethsone Phosphate (DP)) with or without 0.5 mg/ml EDTA, respectively, were manufactured and put on stability (50 ml amber vial; 0, 1, 3, 6 months at 40°C/75%RH). All 6 formulations contained 5% headspace oxygen (95% nitrogen) and lacked sulfite. The results demonstrates that the formulations with an increasing DSP concentration form less total impurities over time. An overview of these results is shown in Table 12.

Table 12

				40°C - Inverted											
	DSP	EDTA		**Description**				**pH**				**Assay (DSP) (95.0-105.0%)**			
Batch #	mg/ml	mg/ml	months	0	1	3	6	0	1	3	6	0	1	3	6
1	10	+		Pass	Pass	Fail	Fail	7.6	7.6	7.6	7.6	99.7	98.2	97.9	96.5
2	10	-		Pass	Pass	Fail	Fail	7.6	7.7	7.7	7.7	98.5	97.6	97.3	95.4
3	30	+		Pass	Fail	Fail	Fail	7.6	7.6	7.6	7.7	95.9	94.7	94.8	93.3
4	30	-		Pass	Pass	Fail	Fail	7.7	7.6	7.6	7.7	94.6	93.5	94.2	92.3
				40°C - Inverted											
	DSP	EDTA		**Description**				**pH**				**Assay (DSP) (95.0-105.0%)**			
Batch #	mg/ml	mg/ml	months	0	1	3	6	0	1	3	6	0	1	3	6
1	45	+		Pass	Pass	Pass	Fail	7.7	7.7	7.7	7.7	97.3	96.8	96.6	95.4
2	45	-		Pass	Pass	Pass	Fail	7.7	7.7	7.6	7.7	97.7	96.9	96.7	96.4

				40°C - Inverted											
	DSP	EDTA		**Impurity A (%)**				**Impurity B (%)**				**Impurity C (%)**			
Batch #	mg/ml	mg/ml	months	0	1	3	6	0	1	3	6	0	1	3	6
1	10	+		<0.05	0.16	0.27	0.58	0.08	0.07	0.06	0.06	0.05	0.11	0.22	0.31
2	10	-		<0.05	0.17	0.31	0.47	0.09	0.07	0.07	0.06	0.05	0.11	0.19	0.24
3	30	+		<0.05	0.16	0.41	0.75	0.08	0.07	0.07	0.07	0.05	0.1	0.18	0.24
4	30	-		<0.05	0.13	0.32	0.64	0.09	0.07	0.07	0.07	0.05	0.1	0.16	0.22
				40°C - Inverted											
	DSP	EDTA		**Impurity A (%)**				**Impurity B (%)**				**Impurity C (%)**			
Batch #	mg/ml	mg/ml	months	0	1	3	6	0	1	3	6	0	1	3	6
1	45	+		<0.05	0.15	0.34	0.62	0.08	0.08	0.08	0.07	0.05	0.1	0.16	0.21
2	45	-		<0.05	0.14	0.37	0.64	0.08	0.08	0.08	0.07	0.05	0.09	0.15	0.19

Table 12 (continued)

				40°C - Inverted											
	DSP	EDTA		**Impurity D (%)**				**Impurity E (%)**				**Impurity F (%)**			
Batch #	mg/ml	mg/ml	months	0	1	3	6	0	1	3	6	0	1	3	6
1	10	+		<0.05	<0.05	0.05	0.14	0.05	<0.05	<0.05	<0.05	<0.05	0.07	0.1	0.13
2	10	-		<0.05	<0.05	0.09	0.23	0.05	<0.05	<0.05	<0.05	<0.05	0.07	0.1	0.14
3	30	+		<0.05	<0.05	0.07	0.18	0.05	<0.05	<0.05	<0.05	<0.05	0.07	0.09	0.12
4	30	-		<0.05	<0.05	0.07	0.2	<0.05	<0.05	<0.05	<0.05	<0.05	0.07	0.09	0.13
				40°C - Inverted											
	DSP	EDTA		**Impurity D (%)**				**Impurity E (%)**				**Impurity F (%)**			
Batch #	mg/ml	mg/ml	months	0	1	3	6	0	1	3	6	0	1	3	6
1	45	+		<0.05	<0.05	0.08	0.2	0.05	<0.05	<0.05	<0.05	<0.05	0.07	0.09	0.12
2	45	-		<0.05	<0.05	0.09	0.21	0.05	<0.05	<0.05	<0.05	<0.05	0.07	0.09	0.13

				40°C - Inverted											
	DSP	EDTA		**Impurity G (%)**				**Unspecified Impurity (%)**				**Total Impurities (%)**			
Batch #	mg/ml	mg/ml	months	0	1	3	6	0	1	3	6	0	1	3	6
1	10	+		0.16	0.16	0.22	0.23	0.11	0.11	0.11	0.11	0.4	0.7	1.3	2.1
2	10	-		0.15	0.16	0.22	0.29	0.11	0.11	0.1	0.1	0.4	0.7	1.2	1.9
3	30	+		0.16	0.17	0.18	0.2	0.11	0.11	0.11	0.11	0.4	0.7	1.2	1.9
4	30	-		0.16	0.18	0.18	0.2	0.11	0.11	0.11	0.1	0.4	0.7	1.1	1.7
				40°C - Inverted											
	DSP	EDTA		**Impurity G (%)**				**Unspecified Impurity (%)**				**Total Impurities (%)**			
Batch #	mg/ml	mg/ml	months	0	1	3	6	0	1	3	6	0	1	3	6
1	45	+		0.16	0.17	0.17	0.18	0.11	0.11	0.11	0.1	0.4	0.7	1.1	1.7
2	45	-		0.16	0.17	0.18	0.2	0.11	0.1	0.11	0.1	0.4	0.7	1.1	1.6

[0265] Fig. 45 & Fig 46: Results of the additional design of experiment for increasing concentrations of the active pharmaceutical ingredient (API) in the AVM0703 formulation: Dexamethasone Sodium Phosphate (DSP). Six formulations with 3 varying levels of DSP (10, 30 and 45 mg/ml) with or without 0.5 mg/ml EDTA, respectively, were manufactured and put on stability (50 ml amber vial; 0, 1, 3, 6 months at 40°C/75%RH). All 6 formulations contained 5% headspace oxygen (95% nitrogen) and lacked sulfite. While there is a clear decrease of impurities C and G for all formulations over 6 months, there seems to be no clear trend for impurity A in the formulations including EDTA or impurity D in the formulations lacking EDTA. For impurity A in the formulation lacking EDTA there is an initital increase visible that eventually stagnates, while for impurity D in the formulations including EDTA there is a visible increase over time up to ~0.2%.

Fig. 47: Design of experiment result (0, 1, 3, 6 months at 40°C/75%RH) for increasing concentrations of the active pharmaceutical ingredient (API) in the AVM0703 formulation: Dexamethasone Sodium Phosphate (DSP). Six formulations with 3 varying levels of DSP (10, 30 and 45 mg/ml, equivalent to 9.15, 27.45 and 41.17 Dexamethsone Phosphate), with or without 0.5 mg/ml EDTA and each containing 5% headspace oxygen (95% nitrogen) were tested for stability. All six formulations lacked sulfite. The top chart includes all formulations, while the middle and bottom each depict the 3 formulations either with (middle) or without EDTA (bottom). The formulations with the highest DSP content of 45 mg/ml still passed the description at 3 months, while all other failed and showed a precipitate. The result demonstrates that the formulations with an increasing DSP concentration form less total impurities over time, independent of the presence or absence of EDTA.

SUPPLEMENTARY TABLES

TABLE A: Examples of Dexamethasone Sodium Phosphate injectables including excipient / vial profile (U.S.) – For Human Use (US)

PRODUCT NDC	PROPRIETARY NAME	DOSAGE FORM NAME	LABELER NAME	Strength	Unit	Excipients	Vial
0641-0367	Dexamethasone Sodium Phosphate	INJECTION	West-Ward Pharmaceuticals Corp.	10	mg/mL	Sodium Sulfite (1.5 mg in 1 mL) (UNII: VTK01UQK3G); Sodium Citrate (16.5 mg in 1 mL) (UNII: 1Q73Q2JULR); Benzyl Alcohol (10.42 mg in 1 mL) (UNII: LKG8494WBH); Water (UNII: 059QF0KO0R); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)	1 ml
0641-0367-25	Dexamethasone Sodium Phosphate	INJECTION	West-Ward Pharmaceuticals Corp.	10	mg/mL	Sodium Sulfite (1.5 mg in 1 mL) (UNII: VTK01UQK3G); Sodium Citrate (16.5 mg in 1 mL) (UNII: 1Q73Q2JULR); Benzyl Alcohol (10.42 mg in 1 mL) (UNII: LKG8494WBH); Water (UNII: 059QF0KO0R); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)	1 ml
52584-420	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	General Injectables and Vaccines, Inc.	10	mg/mL	Methylparaben (1.5 mg in 1 mL) (UNII: A2I8C7HI9T); Propylparaben (0.2 mg in 1 mL) (UNII: Z8IX2SC1OH); Edetate Disodium (0.11 mg in 1 mL) (UNII: 7FLD9 1C8 6K); Anhydrous Trisodium Citrate (10 mg in 1 mL) (UNII: RS7A450LGA); Water (UNII: 059QF0KO0R); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)	10 ml
54868-6099-0	DEXAMETHASONE Sodium Phosphate	INJECTION	Physicians Total Care, Inc.	10	mg/mL	Anhydrous Trisodium Citrate (10 mg in 1 mL) (UNII: RS7A450LGA); Sodium Metabisulfite (1 mg in 1 mL) (UNII: 4VON5FNS3C); Benzyl Alcohol (10 mg in 1 mL) (UNII: LKG8494WBH); Water (UNII: 059QF0KO0R); Citric Acid Monohydrate (UNII: 2968PHW8QP)	10 ml

PRODUCT NDC	PROPRIETARY NAME	DOSAGE FORM NAME	LABELER NAME	Strength	Unit	Excipients	Vial
55154-5118	Dexamethasone Sodium Phosphate	INJECTION	Cardinal Health	10	mg/mL	Sodium Sulfite Anhydrous (1.5 mg in 1 mL) (UNII: 36KCS0R750); Anhydrous Trisodium Citrate (16.5 mg in 1 mL) (UNII: RS7A450LGA); Benzyl Alcohol (10.42 mg in 1 mL) (UNII: LKG8494WBH); Water (UNII: 059QF0KO0R); Sodium Hydroxide (UNII: 55X04QC321); Citric Acid Monohydrate (UNII: 2968PHW8QP)	1 ml
55154-9371	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	Cardinal Health	10	mg/mL	Sodium Citrate, Unspecified Form (24.75 mg in 1 mL) (UNII: 1Q73Q2JULR); Citric Acid Monohydrate (UNII: 2968PHW8QP); Sodium Hydroxide (UNII: 55X04QC321)	1 ml
63323-506-01	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	Fresenius Kabi USA, LLC	10	mg/mL	Sodium Citrate (24.75 mg in 1 mL) (UNII: 1Q73Q2JULR); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)	1 ml
63323-516-10	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	Fresenius Kabi USA, LLC	10	mg/mL	Sodium Citrate (13.5 mg in 1 mL) (UNII: 1Q73Q2JULR); Benzyl Alcohol (10 mg in 1 mL) (UNII: LKG8494WBH); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)	10 ml
67457-420-00	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	Mylan Institutional LLC	10	mg/mL	Methylparaben (1.5 mg in 1 mL) (UNII: A2I8C7HI9T); Propylparaben (0.2 mg in 1 mL) (UNII: Z8IX2SC1OH); Edetate Disodium (0.11 mg in 1 mL) (UNII: 7FLD9 1C8 6K); Anhydrous Trisodium Citrate (10 mg in 1 mL) (UNII: RS7A450LGA); Water (UNII: 059QF0KO0R); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)	10 ml
70069-021	Dexamethasone Sodium Phosphate	INJECTION	Somerset Therapeutics, LLC	10	mg/mL	Trisodium Citrate Dihydrate (24.75 mg in 1 mL) (UNII: B22547B95K), Citric Acid Monohydrate (UNII: 2968PHW8QP), Sodium	1 ml

PRODUCT NDC	PROPRIETARY NAME	DOSAGE FORM NAME	LABELER NAME	Strength	Unit	Excipients	Vial
						Hydroxide (UNII: 55X04QC32I), Water (UNII: 059QF0KO0R)	
70518-0532	Dexamethasone Sodium Phosphate	INJECTION	REMEDYREPACK INC.	10	mg/mL	Sodium Sulfite (1.5mg in 1 mL) (UNII: VTK01UQK3G), Sodium Citrate (16.5mg in 1mL) (UNII: 1Q73Q2JULR), Benzyl Alcohol (10.42mg in 1mL) (UNII: LKG8 49 4WBH), Water (UNII: 059QF0KO0R), Sodium Hydoxide (UNII: 55X04QC32I), Citric Acid Monohydrate (UNII: 2968PHW8QP)	1 ml
71872-7090	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	Medical Purchasing Solutions, LLC	10	mg/mL	Methylparaben (1.5 mg in 1 mL) (UNII: A2I8C7HI9T); Propylparaben (0.2 mg in 1 mL) (UNII: Z8IX2SC1OH); Edetate Disodium (0.11 mg in 1 mL) (UNII: 7FLD9 1C8 6K); Anhydrous Trisodium Citrate (10 mg in 1 mL) (UNII: RS7A450LGA); Citric Acid Monohydrate (UNII: 2968PHW8QP); Sodium Hydroxide (UNIIL 55X04QC321); Water (UNII: 059QF0KO0R)	10 ml
71872-7091	Dexamethasone Sodium Phosphate	INJECTION	Medical Purchasing Solutions, LLC	10	mg/mL	Sodium Sulfite (1.5 mg in 1 mL) (UnII: VTK01UQK3G); Sodium Citrate (16.5 mg in 1 mL) (UNII: 1Q73Q2JULR); Benzyl Alcohol (10.42 mg in 1 mL) (UNII: LKG8494WBH); Water (UNII: 059QF0KO0R); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 296PHW8QP)	1 ml
76420-270	DMT SUIK	INJECTION, SOLUTION	Asclemed USA, Inc.	10	mg/mL	Sodium Citrate (UNII: 1Q73Q2JULR), Citric Acid Monohydrate (UNII: 2968PHW8QP), Sodium Hydroxide (UNII: 55X04QC32I)	1 ml
69677-071	MAS CARE-PAK DEXAMETHASONE	KIT	MAS Management Group Inc.	10	mg/mL	SODIUM HYDROXIDE (UNII: 55X04QC32I), SODIUM CITRATE (24.5 mg in 1 mL)(UNII: 1Q73Q2JULR), CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	1 ml

PRODUCT NDC	PROPRIETARY NAME	DOSAGE FORM NAME	LABELER NAME	Strength	Unit	Excipients	Vial
53225-3660	ReadySharp Dexamethasone	INJECTION	Terrain Pharmaceuticals	10	mg/mL	SODIUM SULFITE (1.5 mg in 1 mL) (UNII: VTK01UQK3G), SODIUM CITRATE (16.5 mg in 1 mL) (UNII: 1Q73Q2JULR), BENZYL ALCOHOL (10.42 mg in 1 mL) (UNII: LKG8 49 4WBH), WATER (UNII: 059QF0KO0R), SODIUM HYDROXIDE (UNII: 55X04QC32I), CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	1 ml
76420-810	Mardex 25 Kit	KIT; 1 ml vial part of kit; Size 50060163323-506-0110 mg/mL1 mLPackaged in twenty-fives	Asclemed USA, Inc.	10	mg/mL	Sodium Citrate (UNII: 1Q73Q2JULR), Citric Acid Monohydrate (UNII: 2968PHW8QP), Sodium Hydroxide (UNII: 55X04QC32I)	1 ml vial;
70112-555	TopiDex	KIT	Topicare Management, LLC	10	mg/mL	SODIUM HYDROXIDE (UNII: 55X04QC32I), SODIUM CITRATE (24.5 mg in 1 mL) (UNII: 1Q73Q2JULR), CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	1 ml
0641-6146-01	DEXAMETHASONE SODIUM PHOSPHATE		West-Ward Pharmaceuticals Corp.	4	mg/ml	Sodium Sulfite Anhydrous (1 mg/ml), sodium citrate anhydrous (19.4 mg/ml) and (0.01 mL) benzyl alcohol 10.42 mg/ml (preservative) in Water for Injection.	5 ml
0006-7646-03 (withdrawn)	DECADRON Phosphate injection	INJECTION, SOLUTION	Merck	24	mg/ml	8 mg/ml creatinine, 10 mg/ml sodium citrate, 0.5 mg/ml disodium edetate, sodium hydroxide to adjust pH, and Water for Injection q.s., with 1 mg/ml sodium bisulfite, 1.5 mg/ml methylparaben, and 0.2 mg/ml propylparaben added as preservatives.	5 ml

TABLE B: Examples of Dexamethasone Sodium Phosphate formulations including excipient profile (U.S.)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
64679-810	Baycadron	ELIXIR	ORAL	ANDA 088254	Wockhardt USA, LLC	0.5	mg/5mL	Benzoic Acid, USP (as preservative) (0.1%); Alcohol (5.1%), raw sugar (UNII: 8M707QY5GH), propylene glycol (UNII: 6DC9Q167V3), benzoic acid (UNII: 8SKN0B0MIM), alcohol (UNII: 3K9958V90M), Anhydrous Citric Acid (UNII: XF417D3PSL), FD&C red no. 40 (UNII: WZB9127XOA), water (UNII: 059QF0KO0R), sodium citrate (UNII: 1Q73Q2JULR), citric acid monohydrate (UNII: 2968PHW8QP)
58463-010	Decadron	ELIXIR	ORAL	ANDA 090891	Pragma Pharmaceuticals, LLC	0.5	mg/5mL	Benzoic Acid, USP (as preservative) (0.1%); Alcohol (% v/v) (5.1%), alcohol (UNII: 3K9958V90M), benzoic acid (UNII: 8SKN0B0MIM), citric acid monohydrate (UNII: 2968PHW8QP), FD&C red no. 40 (UNII: WZB9127XOA), propylene glycol (UNII: 6DC9Q167V3), raspberry (UNII: 4N14V5R27W), sucrose (UNII: C151H8M554), trisodium citrate dihydrate (UNII: B22547B95K), water (UNII: 059QF0KO0R)
58463-014	Decadron	TABLET	ORAL	ANDA 088481	Pragma Pharmaceuticals, LLC	0.5	mg/1	anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP); D&C Yellow No. 10 (UNII: 35SW5USQ3G); FD&C Yellow No. 5 (UNII: 1753WB2F1M)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
58463-015	Decadron	TABLET	ORAL	ANDA 088481	Pragma Pharmaceuticals, LLC	0.75	mg/1	anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP); D&C Yellow No. 10 (UNII: 35SW5USQ3G); FD&C Blue No. 1 (UNII: H3R473TBD)
58463-016	Decadron	TABLET	ORAL	ANDA 088481	Pragma Pharmaceuticals, LLC	4	mg/1	anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
58463-017	Decadron	TABLET	ORAL	ANDA 088481	Pragma Pharmaceuticals, LLC	6	mg/1	anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
0054-4179	Dexamethasone	TABLET	ORAL	ANDA 084611	West-Ward Pharmaceuticals Corp.	0.5	mg/1	D&C Yellow No. 10 (0.5 mg and 4 mg) (UNII: 35SW5USQ3G); FD&C Yellow No. 6 (0.5 mg and 4 mg) (UNII: H77VE193A8); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
0054-4180	Dexamethasone	TABLET	ORAL	ANDA 084613	West-Ward Pharmaceuticals Corp.	0.75	mg/1	FD&C Blue No. 1 (0.75 mg and 1.5 mg) (UNII: H3R47K3TBD); Lactose Monohydrate (UNII: EWQ57Q815X);

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
								Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
0054-4181	Dexamethasone	TABLET	ORAL	ANDA 088306	West-Ward Pharmaceuticals Corp.	1	mg/1	Ferric Oxide Yellow (1 mg) (UNII: EX438O2MRT); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
0054-4182	Dexamethasone	TABLET	ORAL	ANDA 084610	West-Ward Pharmaceuticals Corp.	1.5	mg/1	FD&C Blue No. 1 (0.75 mg and 1.5 mg) (UNII: H3R47K3TBD); FD&C Red No. 3 (1.5 mg) (UNII: PN2ZH5LOQY); FD&C Red No. 40 (1.5 mg) (UNII: WZB9127XOA); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
0054-4183	Dexamethasone	TABLET	ORAL	ANDA 087916	West-Ward Pharmaceuticals Corp.	2	mg/1	Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
0054-4184	Dexamethasone	TABLET	ORAL	ANDA 084612	West-Ward Pharmaceuticals Corp.	4	mg/1	D&C Yellow No. 10 (0.5 mg and 4 mg) (UNII: 35SW5USQ3G); FD&C Yellow No. 6 (0.5 mg and 4 mg) (UNII: H77VE193A8); FD&C Green No. 3 (4 mg and 6 mg) (UNII: 3P3ONR6O1S); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
0054-4186	Dexamethasone	TABLET	ORAL	ANDA 088316	West-Ward Pharmaceuticals Corp.	6	mg/1	FD&C Green No. 3 (4 mg and 6 mg) (UNII: 3P3ONR6O1S); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Com (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
0054-8174	Dexamethasone	TABLET	ORAL	ANDA 088306	West-Ward Pharmaceuticals Corp.	1	mg/1	Ferric Oxide Yellow (1 mg) (UNII: EX438O2MRT); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
0054-8175	Dexamethasone	TABLET	ORAL	ANDA 084612	West-Ward Pharmaceuticals Corp.	4	mg/1	D&C Yellow No. 10 (0.5 mg and 4 mg) (UNII: 35SW5USQ3G); FD&C Yellow No. 6 (0.5 mg and 4 mg) (UNII: H77VE193A8); FD&C Green No. 3 (4 mg and 6 mg) (UNII: 3P3ONR6O1S); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Com (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
0054-8176	Dexamethasone	TABLET	ORAL	ANDA 087916	West-Ward Pharmaceuticals Corp.	2	mg/1	Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Com (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
0054-8179	Dexamethasone	TABLET	ORAL	ANDA 084611	West-Ward Pharmaceuticals Corp.	0.5	mg/1	D&C Yellow No. 10 (0.5 mg and 4 mg) (UNII: 35SW5USQ3G); FD&C Yellow No. 6 (0.5 mg and 4 mg) (UNII: H77VE193A8); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch,

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
								Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
0054-8180	Dexamethasone	TABLET	ORAL	ANDA 084613	West-Ward Pharmaceuticals Corp.	0.75	mg/1	FD&C Blue No. 1 (0.75 mg and 1.5 mg) (UNII: H3R47K3TBD); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
0054-8181	Dexamethasone	TABLET	ORAL	ANDA 084610	West-Ward Pharmaceuticals Corp.	1.5	mg/1	FD&C Blue No. 1 (0.75 mg and 1.5 mg) (UNII: H3R47K3TBD); FD&C Red No. 3 (1.5 mg) (UNII: PN2ZH5LOQY); FD&C Red No. 40 (1.5 mg) (UNII: WZB9127XOA); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
0054-8183	Dexamethasone	TABLET	ORAL	ANDA 088316	West-Ward Pharmaceuticals Corp.	6	mg/1	FD&C Green No. 3 (4 mg and 6 mg) (UNII: 3P3ONR6O1S); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
0095-0087	Dexamethasone	TABLET	ORAL	ANDA 040700	ECR Pharmaceuticals	1.5	mg/1	microcrystalline cellulose (UNII: OP1R32D61U); anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); FD&C Red No. 40 aluminum lake

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
0095-0088	Dexamethasone	TABLET	ORAL	ANDA 040700	ECR Pharmaceuticals	1.5	mg/1	microcrystalline cellulose (UNII: OP1R32D61U); anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); FD&C Red No. 40 aluminum lake
0095-0089	Dexamethasone	TABLET	ORAL	ANDA 040700	ECR Pharmaceuticals	1.5	mg/1	microcrystalline cellulose (UNII: OP1R32D61U); anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); FD&C Red No. 40 aluminum lake
10544-211	Dexamethasone	TABLET	ORAL	ANDA 088237	Blenheim Pharmacal, Inc.	1.5	mg/1	FD&C Red No. 40 (UNII: WZB9127XOA); Magnesium Stearate (UNII:70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); Stearic Acid (UNII: 4ELV7Z65AP)
10544-212	Dexamethasone	TABLET	ORAL	ANDA 088238	Blenheim Pharmacal, Inc.	4	mg/1	Magnesium Stearate (UNII:70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); Stearic Acid (UNII: 4ELV7Z65AP)
21695-290	Dexamethasone	TABLET	ORAL	ANDA 084613	Rebel Distributors Corp	0.75	mg/1	FD&C Blue No. 1 (0.75, 1.5 mg) (UNII: H3R47K3TBD); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch,

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
								Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
21695-382	Dexamethasone	TABLET	ORAL	ANDA 084612	Rebel Distributors Corp	4	mg/1	D&C Yellow No. 10 (0.5, 4 mg) (UNII: 35SW5USQ3G); FD&C Green No. 3 (4, 6 mg) (UNII: 3P3ONR6O1S); FD&C Yellow No. 6 (0.5, 4 mg) (UNII: H77VE193A8); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
21695-728	Dexamethasone	TABLET	ORAL	ANDA 088306	Rebel Distributors Corp	1	mg/1	Ferric Oxide Yellow (1 mg) (UNII: EX438O2MRT); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
21695-745	Dexamethasone	TABLET	ORAL	ANDA 087916	Rebel Distributors Corp	2	mg/1	Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
24236-550	Dexamethasone	TABLET	ORAL	ANDA 084612	REMEDYREPACK INC.	4	mg/1	D&C Yellow No. 10 (0.5 mg and 4 mg) (UNII: 35SW5USQ3G); FD&C Green No. 3 (4 mg and 6 mg) (UNII: 3P3ONR6O1S); FD&C Yellow No. 6 (0.5 mg and 4 mg) (UNII: H77VE193A8); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
33261-625	Dexamethasone	TABLET	ORAL	ANDA 088238	Aidarex Pharmaceuticals LLC	4	mg/1	anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
42195-015	Dexamethasone	TABLET	ORAL	ANDA 088237	Xspire Pharma, LLC	1.5	mg/1	FD&C Red No. 40 (UNII: WZB9127XOA); Magnesium Stearate (UNII:70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); Stearic Acid (UNII: 4ELV7Z65AP)
43063-266	Dexamethasone	TABLET	ORAL	ANDA 087916	PD-Rx Pharmaceuticals, Inc.	2	mg/1	Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
48102-045	Dexamethasone	TABLET	ORAL	ANDA 088481	Fera Pharmaceuticals, LLC	0.5	mg/1	D&C Yellow No. 10 (UNII: 35SW5USQ3G); FD&C Yellow No. 5 (UNII: 1753WB2F1M) anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
48102-046	Dexamethasone	TABLET	ORAL	ANDA 088481	Fera Pharmaceuticals, LLC	0.75	mg/1	D&C Yellow No. 10 (UNII: 35SW5USQ3G); FD&C Blue No. 1 (UNII: H3R47K3TBD) anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48);

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
								magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
48102-047	Dexamethasone	TABLET	ORAL	ANDA088481	Fera Pharmaceuticals, LLC	4	mg/1	anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
48102-048	Dexamethasone	TABLET	ORAL	ANDA088481	Fera Pharmaceuticals, LLC	6	mg/1	anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
49884-084	Dexamethasone	TABLET	ORAL	ANDA088148	Par Pharmaceutical Inc.	0.5	mg/1	D&C Yellow No. 10 (UNII: 35SW5USQ3G); FD&C Yellow No. 5 (UNII: 1753WB2F1M) anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
49884-085	Dexamethasone	TABLET	ORAL	ANDA088160	Par Pharmaceutical Inc.	0.75	mg/1	D&C Yellow No. 10 (UNII: 35SW5USQ3G); FD&C Blue No. 1 (UNII: H3R47K3TBD) anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
								cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
49884-086	Dexamethasone	TABLET	ORAL	ANDA088237	Par Pharmaceutical Inc.	1.5	mg/1	FD&C Red No. 40 (UNII: WZB9127XOA); anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
49884-087	Dexamethasone	TABLET	ORAL	ANDA088238	Par Pharmaceutical Inc.	4	mg/1	anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
49884-373	Dexamethasone	TABLET	ORAL	ANDA088481	Par Pharmaceutical Inc.	6	mg/1	D&C Yellow No. 10 (UNII: 35SW5USQ3G); FD&C Blue No. 1 (UNII: H3R47K3TBD); FD&C Yellow No. 6 (UNII: H77VE193A8); anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
49999-059	Dexamethasone	TABLET	ORAL	ANDA084612	Lake Erie Medical DBA Quality Care Products LLC	4	mg/1	D&C Yellow No. 10 (0.5, 4 mg) (UNII: 35SW5USQ3G); FD&C Green No. 3 (4, 6 mg) (UNII: 3P3ONR6O1S); FD&C Yellow No. 6 (0.5, 4 mg) (UNII: H77VE193A8); Lactose Monohydrate

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
								(UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
50090-0088	Dexamethasone	TABLET	ORAL	ANDA084612	A-S Medication Solutions	4	mg/1	D&C Yellow No. 10 (0.5 mg and 4 mg) (UNII: 35SW5USQ3G); FD&C Green No. 3 (4 mg and 6 mg) (UNII: 3P3ONR6O1S); FD&C Yellow No. 6 (0.5 mg and 4 mg) (UNII: H77VE193A8); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
50090-0089	Dexamethasone	TABLET	ORAL	ANDA084612	A-S Medication Solutions	4	mg/1	D&C Yellow No. 10 (0.5 mg and 4 mg) (UNII: 35SW5USQ3G); FD&C Green No. 3 (4 mg and 6 mg) (UNII: 3P3ONR6O1S); FD&C Yellow No. 6 (0.5 mg and 4 mg) (UNII: H77VE193A8); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
52959-547	Dexamethasone	TABLET	ORAL	ANDA088238	H.J. Harkins Company, Inc.	4	mg/1	anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
53217-231	Dexamethasone	TABLET	ORAL	ANDA 084613	Aidarex Pharmaceuticals LLC	0.75	mg/1	FD&C Blue No. 1 (0.75 mg and 1.5 mg) (UNII: H3R47K3TBD); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
53217-310	Dexamethasone	ELIXIR	ORAL	ANDA 084754	Aidarex Pharmaceuticals LLC	0.5	mg/5mL	Benzoic Acid, USP (as preservative) (0.1%); Alcohol (5%)
54868-0218	Dexamethasone	TABLET	ORAL	ANDA 084612	Physicians Total Care, Inc	4	mg/1	D&C Yellow No. 10 (0.5, 4 mg) (UNII: 35SW5USQ3G); FD&C Green No. 3 (4, 6 mg) (UNII: 3P3ONR6O1S); FD&C Yellow No. 6 (0.5, 4 mg) (UNII: H77VE193A8); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
54868-0916	Dexamethasone	TABLET	ORAL	ANDA 084613	Physicians Total Care, Inc	0.75	mg/1	FD&C Blue No. 1 (0.75, 1.5 mg) (UNII: H3R47K3TBD); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
54868-0927	Dexamethasone	TABLET	ORAL	ANDA 084611	Physicians Total Care, Inc	0.5	mg/1	D&C Yellow No. 10 (0.5, 4 mg) (UNII: 35SW5USQ3G); FD&C Yellow No. 6 (0.5, 4 mg) (UNII: H77VE193A8); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
54868-1744	Dexamethasone	TABLET	ORAL	ANDA 084610	Physicians Total Care, Inc	1.5	mg/1	FD&C Blue No. 1 (0.75, 1.5 mg) (UNII: H3R47K3TBD); FD&C Red No. 3 (1.5 mg) (UNII: PN2ZH5LOQY); FD&C Red No. 40 (1.5 mg) (UNII: WZB9127XOA); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
54868-3157	Dexamethasone	TABLET	ORAL	ANDA 087916	Physicians Total Care, Inc	2	mg/1	Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
54868-5334	Dexamethasone	TABLET	ORAL	ANDA 040700	Physicians Total Care, Inc.	1.5	mg/1	anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); FD&C Red No. 40
54868-5903	Dexamethasone	TABLET	ORAL	ANDA 088316	Physicians Total Care, Inc	6	mg/1	FD&C Green No. 3 (4, 6 mg) (UNII: 3P3ONR6O1S); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
54879-003	Dexamethasone	ELIXIR	ORAL	ANDA 084754	STI Pharma LLC	0.5	mg/5mL	Benzoic Acid, USP (as preservative) (0.1%); Alcohol (5%)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
55154-4901	Dexamethasone	TABLET	ORAL	ANDA 084612	Cardinal Health	4	mg/1	D&C Yellow No. 10 (0.5 mg and 4 mg) (UNII: 35SW5USQ3G); FD&C Green No. 3 (4 mg and 6 mg) (UNII: 3P3ONR6O1S); FD&C Yellow No. 6 (0.5 mg and 4 mg) (UNII: H77VE193A8); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Com (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
55154-4914	Dexamethasone	TABLET	ORAL	ANDA 087916	Cardinal Health	2	mg/1	Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Com (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
55289-582	Dexamethasone	TABLET	ORAL	ANDA 084612	PD-Rx Pharmaceuticals, Inc.	4	mg/1	D&C Yellow No. 10 (0.5 mg and 4 mg) (UNII: 35SW5USQ3G); FD&C Green No. 3 (4 mg and 6 mg) (UNII: 3P3ONR6O1S); FD&C Yellow No. 6 (0.5 mg and 4 mg) (UNII: H77VE193A8); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Com (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
55289-903	Dexamethasone	TABLET	ORAL	ANDA 084613	PD-Rx Pharmaceuticals, Inc.	0.75	mg/1	FD&C Blue No. 1 (0.75 mg and 1.5 mg) (UNII: H3R47K3TBD); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Com (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
60432-466	Dexamethasone	ELIXIR	ORAL	ANDA 088254	Morton Grove Pharmaceuticals, Inc.	0.5	mg/5mL	Benzoic Acid, USP (as preservative) (0.1%); Alcohol (5.1%)
61919-269	Dexamethasone	TABLET	ORAL	ANDA 088237	Direct Rx	1.5	mg/1	FD&C Red No. 40 (UNII: WZB9127XOA); anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
63187-383	Dexamethasone	TABLET	ORAL	ANDA 087916	Proficient Rx LP	2	mg/1	Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
63187-561	Dexamethasone	TABLET	ORAL	ANDA 084612	Proficient Rx LP	4	mg/1	D&C Yellow No. 10 (0.5 mg, 4 mg) (UNII: 35SW5USQ3G); FD&C Green No. 3 (4 mg, 6 mg) (UNII: 3P3ONR6O1S); FD&C Yellow No. 6 (0.5 mg, 4 mg) (UNII: H77VE193A8); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
63629-3742	Dexamethasone	TABLET	ORAL	ANDA 084612	Bryant Ranch Prepack	4	mg/1	D&C Yellow No. 10 (0.5, 4 mg) (UNII: 35SW5USQ3G); FD&C Green No. 3 (4, 6 mg) (UNII: 3P3ONR6O1S); FD&C Yellow No. 6 (0.5, 4 mg) (UNII: H77VE193A8); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch,

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
								Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
63629-4129	Dexamethasone	TABLET	ORAL	ANDA 084613	Bryant Ranch Prepack	0.75	mg/1	FD&C Blue No. 1 (0.75 mg and 1.5 mg) (UNII: H3R47K3TBD); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
64980-509	Dexamethasone	ELIXIR	ORAL	ANDA 090891	Rising Pharmaceuticals, Inc.	0.5	mg/5mL	Benzoic Acid, USP (as preservative) (0.1%); Alcohol (% v/v) (5%)
66267-067	Dexamethasone	TABLET	ORAL	ANDA 088238	NuCare Pharmaceuticals, Inc.	4	mg/1	anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
66336-479	Dexamethasone	TABLET	ORAL	ANDA 084612	Dispensing Solutions, Inc.	4	mg/1	D&C Yellow No. 10 (0.5, 4 mg) (UNII: 35SW5USQ3G); FD&C Green No. 3 (4, 6 mg) (UNII: 3P3ONR6O1S); FD&C Yellow No. 6 (0.5, 4 mg) (UNII: H77VE193A8); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
67296-0326	Dexamethasone	TABLET	ORAL	ANDA 084612	RedPharm Drug	4	mg/1	D&C Yellow No. 10 (0.5 mg and 4 mg) (UNII: 35SW5USQ3G); FD&C Green No. 3 (4 mg and 6 mg) (UNII: 3P3ONR6O1S); FD&C Yellow No. 6 (0.5 mg and 4 mg) (UNII: H77VE193A8); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
67296-1090	Dexamethasone	TABLET	ORAL	ANDA 088238	RedPharm Drug, Inc.	4	mg/1	anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
68047-702	Dexamethasone	TABLET	ORAL	ANDA 201270	Larken Laboratories, Inc.	1.5	mg/1	Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Maltodextrin (UNII:7CVR7L4A2D); Starch, Corn (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
68071-4127	Dexamethasone	TABLET	ORAL	ANDA 088238	NuCare Pharmaceuticals,Inc.	4	mg/1	anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
68788-7142	Dexamethasone	TABLET	ORAL	ANDA 084612	Preferred Pharmaceuticals Inc.	4	mg/1	D&C Yellow No. 10 (0.5 mg and 4 mg) (UNII: 35SW5USQ3G); FD&C Green No. 3 (4 mg and 6 mg) (UNII: 3P3ONR6O1S); FD&C Yellow No. 6

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
								(0.5 mg and 4 mg) (UNII: H77VE193A8); Lactose Monohydrate (UNII: EWQ57Q815X); Magnesium Stearate (UNII:70097M6130); Starch, Com (UNII: 0823NY3SJ); Sucrose (UNII: C151H8M554)
68788-9938	Dexamethasone	TABLET	ORAL	ANDA088238	Preferred Pharmaceuticals, Inc.	4	mg/1	anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
68788-9939	Dexamethasone	TABLET	ORAL	ANDA088160	Preferred Pharmaceuticals, Inc.	0.75	mg/1	D&C Yellow No. 10 (UNII: 35SW5USQ3G); FD&C Blue No. 1 (UNII: H3R47K3TBD) anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
69189-4186	Dexamethasone	TABLET	ORAL	ANDA088316	Avera McKennan Hospital	6	mg/1	
70518-0843	Dexamethasone	TABLET	ORAL	ANDA088238	REMEDYREPACK INC.	4	mg/1	anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
71335-0077	Dexamethasone	TABLET	ORAL	ANDA 088160	Bryant Ranch Prepack	0.75	mg/1	D&C Yellow No. 10 (UNII: 35SW5USQ3G); FD&C Blue No. 1 (UNII: H3R47K3TBD) anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
71335-0177	Dexamethasone	TABLET	ORAL	ANDA 088238	Bryant Ranch Prepack	4	mg/1	anhydrous lactose (UNII: 3SY5LH9PMK); croscarmellose sodium (UNII: M28OL1HH48); magnesium stearate (UNII: 70097M6130); microcrystalline cellulose (UNII: OP1R32D61U); stearic acid (UNII: 4ELV7Z65AP)
0054-3176	Dexamethasone Intensol	SOLUTION, CONCENTRATE	ORAL	ANDA 088252	West-Ward Pharmaceuticals Corp.	1	mg/mL	Alcohol (UNII: 3K9 9 58V9 0M) Benzoic Acid (UNII: 8 SKN0B0MIM), Citric Acid MONOHYDRATE (UNII: 29 6 8 PHW8QP), Edetate Disodium (UNII: 7FLD9 1C8 6K), Propylene Glycol (UNII: 6DC9Q16 7V3), Water (UNII: 0 59QF0KO0R)
68151-5026	Dexamethasone Intensol	SOLUTION, CONCENTRATE	ORAL	ANDA 088252	Carilion Materials Management	1	mg/mL	Alcohol (UNII: 3K9 9 58V9 0M); Benzoic Acid (UNII: 8 SKN0B0MIM); Citric Acid MONOHYDRATE (UNII: 29 6 8 PHW8QP); Edetate Disodium (UNII: 7FLD9 1C8 6K); Propylene Glycol (UNII: 6DC9Q16 7V3); Water (UNII: 0 59QF0KO0R)
0641-0367	Dexamethasone Sodium Phosphate	INJECTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 087702	West-Ward Pharmaceuticals Corp.	10	mg/mL	Sodium Sulfite (1.5 mg in 1 mL) (UNII: VTK01UQK3G); Sodium Citrate (16.5 mg in 1 mL) (UNII: 1Q73Q2JULR); Benzyl Alcohol (10.42 mg in 1 mL)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
								(UNII: LKG8494WBH); Water (UNII: 059QF0KO0R); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)
0641-6145	Dexamethasone Sodium Phosphate	INJECTION	INTRA-ARTICULAR; INTRALESIONAL; INTRAMUSCULAR; INTRAVENOUS; SOFT TISSUE	ANDA 084282	West-Ward Pharmaceuticals Corp.	4	mg/mL	Sodium Sulfite (1 mg in 1 mL) (UNII: VTK01UQK3G); Sodium Citrate (19.4 mg in 1 mL) (UNII: 1Q73Q2JULR); Benzyl Alcohol (10.42 mg in 1 mL) (UNII: LKG8494WBH); Water (UNII: 059QF0KO0R); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)
0641-6146	Dexamethasone Sodium Phosphate	INJECTION	INTRA-ARTICULAR; INTRALESIONAL; INTRAMUSCULAR; INTRAVENOUS; SOFT TISSUE	ANDA 084282	West-Ward Pharmaceuticals Corp.	4	mg/mL	Sodium Sulfite (1 mg in 1 mL) (UNII: VTK01UQK3G); Sodium Citrate (19.4 mg in 1 mL) (UNII: 1Q73Q2JULR); Benzyl Alcohol (10.42 mg in 1 mL) (UNII: LKG8494WBH); Water (UNII: 059QF0KO0R); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)
0904-3006	Dexamethasone Sodium Phosphate	SOLUTION / DROPS	OPHTHALMIC	ANDA 040069	Major Pharmaceuticals	1	mg/mL	Benzalkonium Chloride (0.02%) (UNII: F5UM2KM3W7); Creatinine (UNII: 7FLD91C86K); Edetate Disodium (UNII: 7FLD9 1C8 6K); Hydrochloric Acid (UNII: ML9LGA7468); Phenethyl Alcohol (0.25%) (UNII: ML9LGA7468); Polysorbate 80 (UNII: 6OZP39ZG8H); Water (UNII: 0 59QF0KO0R); Sodium Bisulfite (0.1%) (UNII: TZX5469Z6I); Sodium Borate (UNII: 91MBZ8H3QO); Sodium Citrate (UNII: 1Q73Q2JULR)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
11695-1411	Dexamethasone Sodium Phosphate	SOLUTION / DROPS	OPHTHALMIC	ANDA 040069	Butler Animal Health Supply	1	mg/mL	Benzalkonium Chloride (0.02%) (UNII: F5UM2KM3W7); Creatinine (UNII: 7FLD91C86K); Edetate Disodium (UNII: 7FLD9 1C8 6K); Hydrochloric Acid (UNII: ML9LGA7468); Phenethyl Alcohol (0.25%) (UNII: ML9LGA7468); Polysorbate 80 (UNII: 6OZP39ZG8H); Water (UNII: 0 59QF0KO0R); Sodium Bisulfite (0.1%) (UNII: TZX5469Z6I); Sodium Borate (UNII: 91MBZ8H3QO); Sodium Citrate (UNII: 1Q73Q2JULR)
21695-847	Dexamethasone Sodium Phosphate	SOLUTION	OPHTHALMIC	ANDA 088771	Rebel Distributors Corp	1	mg/mL	Benzalkonium Chloride (0.01%) (UNII: F5UM2KM3W7); Sodium Phosphate, Monobasic (UNII: 3980JIH2SW); Sodium Chloride (UNII: 451W47IQ8X); Sodium Phosphate Dibasic (UNII: GR686LBA74); Edetate Disodium (UNII: 7FLD9 1C8 6K); Sodium Phosphate, Monobasic (UNII: 3980JIH2SW); Sodium Phosphate Dibasic (UNII: GR686LBA74); Water (UNII: 0 59QF0KO0R)
24208-720	Dexamethasone Sodium Phosphate	SOLUTION / DROPS	OPHTHALMIC	ANDA 040069	Bausch & Lomb Incorporated	1	mg/mL	Benzalkonium Chloride (0.02%) (UNII: F5UM2KM3W7); Creatinine (UNII: 7FLD91C86K); Edetate Disodium (UNII: 7FLD9 1C8 6K); Hydrochloric Acid (UNII: ML9LGA7468); Phenethyl Alcohol (0.25%) (UNII: ML9LGA7468); Polysorbate 80 (UNII: 6OZP39ZG8H); Water (UNII: 0 59QF0KO0R); Sodium Bisulfite (0.1%) (UNII: TZX5469Z6I); Sodium Borate (UNII: 91MBZ8H3QO); Sodium Citrate, Unspecified Form (UNII: 1Q73Q2JULR)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
42254-088	Dexamethasone Sodium Phosphate	SOLUTION / DROPS	OPHTHALMIC	ANDA 040069	Rebel Distributors Corp	1	mg/mL	Benzalkonium Chloride (0.02%) (UNII: F5UM2KM3W7); Creatinine (UNII: 7FLD91C86K); Edetate Disodium (UNII: 7FLD9 1C8 6K); Hydrochloric Acid (UNII: ML9LGA7468); Phenethyl Alcohol (0.25%) (UNII: ML9LGA7468); Polysorbate 80 (UNII: 6OZP39ZG8H); Water (UNII: 0 59QF0KO0R); Sodium Bisulfite (0.1%) (UNII: TZX5469Z6I); Sodium Borate (UNII: 91MBZ8H3QO); Sodium Citrate (UNII: 1Q73Q2JULR)
52584-420	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 040802	General Injectables and Vaccines, Inc.	10	mg/mL	Methylparaben (1.5 mg in 1 mL) (UNII: A2I8C7HI9T); Propylparaben (0.2 mg in 1 mL) (UNII: Z8IX2SC1OH); Edetate Disodium (0.11 mg in 1 mL) (UNII: 7FLD9 1C8 6K); Anhydrous Trisodium Citrate (10 mg in 1 mL) (UNII: RS7A450LGA); Water (UNII: 059QF0KO0R); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)
52584-421	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRA-ARTICULAR; INTRALESIONAL; INTRAMUSCULAR; INTRAVENOUS; SOFT TISSUE	ANDA 040803	General Injectables and Vaccines, Inc	4	mg/mL	Methylparaben (1.5 mg in 1 mL) (UNII: A2I8C7HI9T); Propylparaben (0.2 mg in 1 mL) (UNII: Z8IX2SC1OH); Edetate Disodium (0.11 mg in 1 mL) (UNII: 7FLD9 1C8 6K); Anhydrous Trisodium Citrate (10 mg in 1 mL) (UNII: RS7A450LGA); Water (UNII: 059QF0KO0R); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
52584-422	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRA-ARTICULAR; INTRALESIONAL; INTRAMUSCULAR; INTRAVENOUS; SOFT TISSUE	ANDA 040803	General Injectables and Vaccines, Inc	4	mg/mL	Methylparaben (1.5 mg in 1 mL) (UNII: A2I8C7HI9T); Propylparaben (0.2 mg in 1 mL) (UNII: Z8IX2SC1OH); Edetate Disodium (0.11 mg in 1 mL) (UNII: 7FLD9 1C8 6K); Anhydrous Trisodium Citrate (10 mg in 1 mL) (UNII: RS7A450LGA); Water (UNII: 059QF0KO0R); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)
54868-3129	Dexamethasone Sodium Phosphate	SOLUTION	OPHTHALMIC	ANDA 088771	Physicians Total Care, Inc.	1	mg/mL	Benzalkonium Chloride (0.01%) (UNII: F5UM2KM3W7); Sodium Phosphate, Monobasic (UNII: 3980JIH2SW); Sodium Chloride (UNII: 451W47IQ8X); Sodium Phosphate Dibasic (UNII: GR686LBA74); Edetate Disodium (UNII: 7FLD9 1C8 6K); Water (UNII: 0 59QF0KO0R)
54868-6099	DEXAMETHASONE Sodium Phosphate	INJECTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 081126	Physicians Total Care, Inc.	10	mg/mL	Anhydrous Trisodium Citrate (10 mg in 1 mL) (UNII: RS7A450LGA); Sodium Metabisulfite (1 mg in 1 mL) (UNII: 4VON5FNS3C); Benzyl Alcohol (10 mg in 1 mL) (UNII: LKG8494WBH); Water (UNII: 059QF0KO0R); Citric Acid Monohydrate (UNII: 2968PHW8QP)
55045-1755	Dexamethasone Sodium Phosphate	SOLUTION	OPHTHALMIC	ANDA 088771	Dispensing Solutions, Inc.	1	mg/mL	Benzalkonium Chloride (0.01%) (UNII: F5UM2KM3W7); Sodium Phosphate, Monobasic (UNII: 3980JIH2SW); Sodium Chloride (UNII: 451W47IQ8X); Sodium Phosphate Dibasic (UNII: GR686LBA74); Edetate Disodium (UNII: 7FLD9 1C8 6K); Water (UNII: 0 59QF0KO0R)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
55150-237	DEXAMETHASONE SODIUM PHOSPHATE	INJECTION, SOLUTION	INTRA-ARTICULAR; INTRALESIONAL; INTRAMUSCULAR; INTRAVENOUS; SOFT TISSUE	ANDA 206781	AuroMedics Pharma LLC	4	mg/mL	Anhydrous Trisodium Citrate (UNII: RS7A450LGA); Sodium Sulfite (1 mg in 1 mL) (UNII: VTK01UQK3G); Benzyl Alcohol (10 mg in 1 mL) (UNII: LKG8494WBH); Water (UNII: 059QF0KO0R); Anhydrous Citric Acid (UNII: XF417D3PSL); Sodium Hydroxide (UNII: 55X04QC321)
55150-238	DEXAMETHASONE SODIUM PHOSPHATE	INJECTION, SOLUTION	INTRA-ARTICULAR; INTRALESIONAL; INTRAMUSCULAR; INTRAVENOUS; SOFT TISSUE	ANDA 206781	AuroMedics Pharma LLC	4	mg/mL	Anhydrous Trisodium Citrate (UNII: RS7A450LGA); Sodium Sulfite (1 mg in 1 mL) (UNII: VTK01UQK3G); Benzyl Alcohol (10 mg in 1 mL) (UNII: LKG8494WBH); Water (UNII: 059QF0KO0R); Anhydrous Citric Acid (UNII: XF417D3PSL); Sodium Hydroxide (UNII: 55X04QC321)
55150-239	DEXAMETHASONE SODIUM PHOSPHATE	INJECTION, SOLUTION	INTRA-ARTICULAR; INTRALESIONAL; INTRAMUSCULAR; INTRAVENOUS; SOFT TISSUE	ANDA 206781	AuroMedics Pharma LLC	4	mg/mL	Anhydrous Trisodium Citrate (UNII: RS7A450LGA); Sodium Sulfite (1 mg in 1 mL) (UNII: VTK01UQK3G); Benzyl Alcohol (10 mg in 1 mL) (UNII: LKG8494WBH); Water (UNII: 059QF0KO0R); Anhydrous Citric Acid (UNII: XF417D3PSL); Sodium Hydroxide (UNII: 55X04QC321)
55154-5118	Dexamethasone Sodium Phosphate	INJECTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 087702	Cardinal Health	10	mg/mL	Sodium Sulfate Anhydrous (1.5 mg in 1 mL) (UNII: 36KCS0R750); Anhydrous Trisodium Citrate (16.5 mg in 1 mL) (UNII: RS7A450LGA); Benzyl Alcohol (10.42 mg in 1 mL) (UNII: LKG8494WBH); Water (UNII: 059QF0KO0R); Sodium Hydroxide

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
								(UNII: 55X04QC321); Citric Acid Monohydrate (UNII: 2968PHW8QP)
55154-7075	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRA-ARTICULAR; INTRALESIONAL; INTRAMUSCULAR; INTRAVENOUS; SOFT TISSUE	ANDA040803	Cardinal Health	4	mg/mL	Methylparaben (1.5 mg in 1 mL) (UNII: A2I8C7HI9T); Propylparaben (0.2 mg in 1 mL) (UNII: Z8IX2SC1OH); Edetate Disodium (0.11 mg in 1 mL) (UNII: 7FLD9 1C8 6K); Anhydrous Trisodium Citrate (10 mg in 1 mL) (UNII: RS7A450LGA); Water (UNII: 059QF0KO0R); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)
55154-9364	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRAMUSCULAR; INTRAVENOUS	ANDA084916	Cardinal Health	4	mg/mL	Sodium Citrate, Unspecified Form (11 mg in 1 mL) (UNII: 1Q73Q2JULR); Sodium Sulfite (1 mg in 1 mL) (UNII: VTK01UQK3G); Benzyl Alcohol (10 mg in 1 mL) (UNII: LKG8494WBH); Citric Acid Monohydrate (UNII: 2968PHW8QP); Sodium Hydroxide (UNII: 55X04QC321)
55154-9371	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRAMUSCULAR; INTRAVENOUS	ANDA040491	Cardinal Health	10	mg/mL	Sodium Citrate, Unspecified Form (24.75 mg in 1 mL) (UNII: 1Q73Q2JULR); Citric Acid Monohydrate (UNII: 2968PHW8QP); Sodium Hydroxide (UNII: 55X04QC321)
57319-065	Dexamethasone Sodium Phosphate	SOLUTION / DROPS	OPHTHALMIC	ANDA040069	Phoenix Pharmaceutical, Inc.	1	mg/mL	Benzalkonium Chloride (0.02%) (UNII: F5UM2KM3W7); Creatinine (UNII: 7FLD91C86K); Edetate Disodium (UNII: 7FLD9 1C8 6K); Hydrochloric Acid (UNII: ML9LGA7468); Phenethyl Alcohol (0.25%) (UNII: ML9LGA7468); Polysorbate 80 (UNII: 6OZP39ZG8H);

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
								Water (UNII: 0 59QF0KO0R); Sodium Bisulfite (0.1%) (UNII: TZX5469Z6I); Sodium Borate (UNII: 91MBZ8H3QO); Sodium Citrate (UNII: 1Q73Q2JULR)
61314-294	Dexamethasone Sodium Phosphate	SOLUTION	OPHTHALMIC	ANDA 088771	Sandoz Inc	1	mg/mL	Benzalkonium Chloride (0.01%) (UNII: F5UM2KM3W7); Sodium Phosphate, Monobasic (UNII: 3980JIH2SW); Sodium Chloride (UNII: 451W47IQ8X); Sodium Phosphate, Dibasic (UNII: GR686LBA74); Edetate Disodium (UNII: 7FLD9 1C8 6K); Water (UNII: 0 59QF0KO0R)
61786-979	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 084916	REMEDYREPACK INC.	4	mg/mL	Sodium Citrate (11 mg in 1 mL) (UNII: 1Q73Q2JULR); Sodium Sulfite (1 mg in 1 mL) (UNII: VTK01UQK3G); Benzyl Alcohol (10 mg in 1 mL) (UNII: LKG8494WBH);Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)
63323-165	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 084916	Fresenius Kabi USA, LLC	4	mg/mL	Sodium Citrate (11 mg in 1 mL) (UNII: 1Q73Q2JULR); Sodium Sulfite (1 mg in 1 mL) (UNII: VTK01UQK3G); Benzyl Alcohol (10 mg in 1 mL) (UNII: LKG8494WBH);Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)
63323-165	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 084916	Fresenius Kabi USA, LLC	4	mg/mL	Sodium Citrate (11 mg in 1 mL) (UNII: 1Q73Q2JULR); Sodium Sulfite (1 mg in 1 mL) (UNII: VTK01UQK3G); Benzyl Alcohol (10 mg in 1 mL) (UNII: LKG8494WBH);Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
63323-506	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 040491	Fresenius Kabi USA, LLC	10	mg/mL	Sodium Citrate (24.75 mg in 1 mL) (UNII: 1Q73Q2JULR); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)
63323-506	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 040491	Fresenius Kabi USA, LLC	10	mg/mL	Sodium Citrate (24.75 mg in 1 mL) (UNII: 1Q73Q2JULR); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)
63323-516	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 040572	Fresenius Kabi USA, LLC	10	mg/mL	Sodium Citrate (13.5 mg in 1 mL) (UNII: 1Q73Q2JULR); Benzyl Alcohol (10 mg in 1 mL) (UNII: LKG8494WBH); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)
67457-420	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 040802	Mylan Institutional LLC	10	mg/mL	Methylparaben (1.5 mg in 1 mL) (UNII: A2I8C7HI9T); Propylparaben (0.2 mg in 1 mL) (UNII: Z8IX2SC1OH); Edetate Disodium (0.11 mg in 1 mL) (UNII: 7FLD9 1C8 6K); Anhydrous Trisodium Citrate (10 mg in 1 mL) (UNII: RS7A450LGA); Water (UNII: 059QF0KO0R); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)
67457-421	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRA-ARTICULAR; INTRALESIONAL; INTRAMUSCULAR; INTRAVENOU	ANDA 040803	Mylan Institutional LLC	4	mg/mL	Methylparaben (1.5 mg in 1 mL) (UNII: A2I8C7HI9T); Propylparaben (0.2 mg in 1 mL) (UNII: Z8IX2SC1OH); Edetate Disodium (0.11 mg in 1 mL) (UNII: 7FLD9 1C8 6K); Anhydrous Trisodium Citrate (10 mg in 1 mL) (UNII: RS7A450LGA); Water (UNII: 059QF0KO0R); Sodium Hydroxide

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
			S; SOFT TISSUE					(UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)
67457-422	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRA-ARTICULAR; INTRALESIONAL; INTRAMUSCULAR; INTRAVENOUS; SOFT TISSUE	ANDA 040803	Mylan Institutional LLC	4	mg/mL	Methylparaben (1.5 mg in 1 mL) (UNII: A2I8C7HI9T); Propylparaben (0.2 mg in 1 mL) (UNII: Z8IX2SC1OH); Edetate Disodium (0.11 mg in 1 mL) (UNII: 7FLD9 1C8 6K); Anhydrous Trisodium Citrate (10 mg in 1 mL) (UNII: RS7A450LGA); Water (UNII: 059QF0KO0R); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)
67457-423	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRA-ARTICULAR; INTRALESIONAL; INTRAMUSCULAR; INTRAVENOUS; SOFT TISSUE	ANDA 040803	Mylan Institutional LLC	4	mg/mL	Methylparaben (1.5 mg in 1 mL) (UNII: A2I8C7HI9T); Propylparaben (0.2 mg in 1 mL) (UNII: Z8IX2SC1OH); Edetate Disodium (0.11 mg in 1 mL) (UNII: 7FLD9 1C8 6K); Anhydrous Trisodium Citrate (10 mg in 1 mL) (UNII: RS7A450LGA); Water (UNII: 059QF0KO0R); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 2968PHW8QP)
68071-1866	DEXAMETHASONE SODIUM PHOSPHATE	INJECTION, SOLUTION	INTRA-ARTICULAR; INTRALESIONAL; INTRAMUSCULAR; INTRAVENOUS; SOFT TISSUE	ANDA 206781	NuCare Pharmaceuticals,Inc.	4	mg/mL	Anhydrous Trisodium Citrate (UNII: RS7A450LGA); Sodium Sulfite (1 mg in 1 mL) (UNII: VTK01UQK3G); Benzyl Alcohol (10 mg in 1 mL) (UNII: LKG8494WBH); Water (UNII: 059QF0KO0R); Anhydrous Citric Acid (UNII: XF417D3PSL); Sodium Hydroxide (UNII: 55X04QC321)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
70069-021	Dexamethasone Sodium Phosphate	INJECTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 207442	Somerset Therapeutics, LLC	10	mg/mL	Trisodium Citrate Dihydrate (24.75 mg in 1 mL) (UNII: B22547B95K), Citric Acid Monohydrate (UNII: 2968PHW8QP), Sodium Hydroxide (UNII: 55X04QC32I), Water (UNII: 059QF0KO0R)
70518-0410	Dexamethasone Sodium Phosphate	SOLUTION / DROPS	OPHTHALMIC	ANDA 040069	REMEDYREPACK INC.	1	mg/mL	BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7), CREATININE (UNII: AYI8EX34EU), EDETATE DISODIUM (UNII: 7FLD91C86K), HYDROCHLORIC ACID (UNII: QTT17582CB), PHENYLETHYL ALCOHOL (UNII: ML9LGA7468), POLYSORBATE 80 (UNII: 6OZP39ZG8H), WATER (UNII: 059QF0KO0R), SODIUM BISULFITE (UNII: TZX5469Z6I), SODIUM BORATE (UNII: 91MBZ8H3QO), SODIUM CITRATE, UNSPECIFIED FORM (UNII: 1Q73Q2JULR)
70518-0532	Dexamethasone Sodium Phosphate	INJECTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 087702	REMEDYREPACK INC.	10	mg/mL	Sodium Sulfite (1.5mg in 1 mL) (UNII: VTK01UQK3G), Sodium Citrate (16.5mg in 1mL) (UNII: 1Q73Q2JULR), Benzyl Alcohol (10.42mg in 1mL) (UNII: LKG8 49 4WBH), Water (UNII: 059QF0KO0R), Sodium Hydoxide (UNII: 55X04QC32I), Citric Acid Monohydrate (UNII: 2968PHW8QP)
70518-0621	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 084916	REMEDYREPACK INC.	4	mg/mL	Sodium Citrate (11 mg in 1 mL) (UNII: 1Q73Q2JULR), Sodium Sulfite (1 mg in 1 mL) (UNII: VTK01UQK3G), Benzyl Alcohol (10 mg in 1 ml) (UNII: LKG8494WBH), Sodium Hydroxide (UNII: 55X04QC32I), Citric Acid Monohydrate (UNII: 2968PHW8QP)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
70518-0872	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 084916	REMEDYREPACK INC.	4	mg/mL	Sodium Citrate (11 mg in 1 mL) (UNII: 1Q73Q2JULR), Sodium Sulfite (1 mg in 1 mL) (UNII: VTK01UQK3G), Benzyl Alcohol (10 mg in 1 ml) (UNII: LKG8494WBH), Sodium Hydroxide (UNII: 55X04QC32I), Citric Acid Monohydrate (UNII: 2968PHW8QP)
71872-7021	DEXAMETHASONE SODIUM PHOSPHATE	INJECTION, SOLUTION	INTRA-ARTICULAR; INTRALESIONAL; INTRAMUSCULAR; INTRAVENOUS; SOFT TISSUE	ANDA 206781	Medical Purchasing Solutions, LLC	4	mg/mL	Benzyl Alcohol (10 mg in 1 mL) (UNII: LKG8494WBH), Sodium Sulfite (1 mg in 1 mL) (UNII: VTK01UQK3G), Anhydrous Trisodium Citrate (UNII: RS7A450LGA), Anhydrous Citric Acid (UNII: XF417D3PSL), Sodium Hydroxide (55X04QC32I), Water (059QF0KO0R)
71872-7090	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 040802	Medical Purchasing Solutions, LLC	10	mg/mL	Methylparaben (1.5 mg in 1 mL) (UNII: A2I8C7HI9T), Propylparaben (0.2 mg in 1 mL) (UNII: Z8IX2SC1OH); Edetate Disodium (0.11 mg in 1 mL) (UNII: 7FLD9 1C8 6K); Anhydrous Trisodium Citrate (10 mg in 1 mL) (UNII: RS7A450LGA); Citric Acid Monohydrate (UNII: 2968PHW8QP); Sodium Hydroxide (UNIIL 55X04QC321); Water (UNII: 059QF0KO0R)
71872-7091	Dexamethasone Sodium Phosphate	INJECTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 087702	Medical Purchasing Solutions, LLC	10	mg/mL	Sodium Sulfite (1.5 mg in 1 mL) (UnII: VTK01UQK3G); Sodium Citrate (16.5 mg in 1 mL) (UNII: 1Q73Q2JULR); Benzyl Alcohol (10.42 mg in 1 mL) (UNII: LKG8494WBH); Water (UNII: 059QF0KO0R); Sodium Hydroxide (UNII: 55X04QC321) Citric Acid Monohydrate (UNII: 296PHW8QP)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
71872-7092	DEXAMETHASONE SODIUM PHOSPHATE	INJECTION, SOLUTION	INTRA-ARTICULAR; INTRALESIONAL; INTRAMUSCULAR; INTRAVENOUS; SOFT TISSUE	ANDA 206781	Medical Purchasing Solutions, LLC	4	mg/mL	Benzyl Alcohol (10 mg in 1 mL) (UNII: LKG8494WBH), Sodium Sulfite (1 mg in 1 mL) (UNII: VTK01UQK3G), Anhydrous Trisodium Citrate (UNII: RS7A450LGA), Anhydrous Citric Acid (UNII: XF417D3PSL), Sodium Hydroxide (55X04QC32I), Water (059QF0KO0R)
71872-7128	DEXAMETHASONE SODIUM PHOSPHATE	INJECTION, SOLUTION	INTRA-ARTICULAR; INTRALESIONAL; INTRAMUSCULAR; INTRAVENOUS; SOFT TISSUE	ANDA 206781	Medical Purchasing Solutions, LLC	4	mg/mL	Benzyl Alcohol (10 mg in 1 mL) (UNII: LKG8494WBH), Sodium Sulfite (1 mg in 1 mL) (UNII: VTK01UQK3G), Anhydrous Trisodium Citrate (UNII: RS7A450LGA), Anhydrous Citric Acid (UNII: XF417D3PSL), Sodium Hydroxide (55X04QC32I), Water (059QF0KO0R)
76045-106	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	INTRA-ARTICULAR; INTRALESIONAL; INTRAMUSCULAR; INTRAVENOUS; SOFT TISSUE	ANDA 203129	Fresenius Kabi USA, LLC	4	mg/mL	Citric Acid Monohydrate (UNII: 2968PHW8QP), Trisodium Citrate Dihydrate (UNII: B22547B95K), Water (UNII: 059QF0KO0R), Sodium Hydroxide (UNII: 55X04QC32I)
51655-012	Dexamethsone	TABLET	ORAL	ANDA 084612	Northwind Pharmaceuticals, LLC	4	mg/1	

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
71879-001	Dexycu	INJECTION, SUSPENSION	INTRAOCULAR	NDA208912	EyePoint Pharmaceuticals US, Inc	517	ug/.005mL	ACETYLTRIETHYL CITRATE (5233 ug in 0.005 mL) (UNII: 5WBR36T90E); Nitrogen (UNII: N762921K75)
76420-270	DMT SUIK	INJECTION, SOLUTION	INTRAMUSCULAR; INTRAVENOUS		Asclemed USA, Inc.	10	mg/mL	Sodium Citrate (UNII: 1Q73Q2JULR), Citric Acid Monohydrate (UNII: 2968PHW8QP), Sodium Hydroxide (UNII: 55X04QC32I)
0998-0615	Maxidex	SUSPENSION	OPHTHALMIC	NDA013422	Alcon Laboratories, Inc.	1	mg/mL	BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7), HYPROMELLOSES (UNII: 3NXW29V3WO), SODIUM CHLORIDE (UNII: 451W47IQ8X), SODIUM PHOSPHATE, DIBASIC (UNII: GR686LBA74), POLYSORBATE 80 (UNII: 6OZP39ZG8H), EDETATE DISODIUM (UNII: 7FLD91C86K), CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP), SODIUM HYDROXIDE (UNII: 55X04QC32I) WATER (UNII: 059QF0KO0R)
71205-013	TaperDex 12-day	TABLET	ORAL	ANDA088237	Proficient Rx LP	1.5	mg/1	ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK), CROSCARMELLOSE SODIUM (UNII: M28OL1HH48), MAGNESIUM STEARATE (UNII: 70097M6I30), MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U), STEARIC ACID (UNII: 4ELV7Z65AP), FD&C RED NO.40 (UNII: WZB9127XOA)
71205-012	TaperDex 6-day	TABLET	ORAL	ANDA088237	Proficient Rx LP	1.5	mg/1	ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK), CROSCARMELLOSE SODIUM (UNII: M28OL1HH48), MAGNESIUM STEARATE (UNII:

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
								70097M6I30), MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U), STEARIC ACID (UNII: 4ELV7Z65AP), FD&C RED NO.40 (UNII: WZB9127XOA)
69677-071	MAS CARE-PAK DEXAMETHASONE	KIT	INTRAMUSCULAR; INTRAVENOUS; TOPICAL	ANDA 040491	MAS Management Group Inc.	10	mg/mL	SODIUM HYDROXIDE (UNII: 55X04QC32I), SODIUM CITRATE (24.5 mg in 1 mL)(UNII: 1Q73Q2JULR), CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)
70529-112	Neuromaquel Neuroma/Anti-Inflammatory System	KIT	INTRA-ARTICULAR; INTRALESIONAL; INTRAMUSCULAR; INTRAVENOUS; SOFT TISSUE	ANDA 084916	IT3 Medical LLC	4	mg/mL	SODIUM CITRATE, UNSPECIFIED FORM (11 mg in 1 mL) (UNII: 1Q73Q2JULR), SODIUM SULFITE (1 mg in 1 mL) (UNII: VTK0 1UQK3G), BENZYL ALCOHOL (10 mg in 1 mL) (UNII: LKG8 49 4WBH), SODIUM HYDROXIDE (UNII: 55X0 4QC32I), CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)
53225-3660	ReadySharp Dexamethasone	INJECTION	INTRAMUSCULAR; INTRAVENOUS	ANDA 087702	Terrain Pharmaceuticals	10	mg/mL	SODIUM SULFITE (1.5 mg in 1 mL) (UNII: VTK01UQK3G), SODIUM CITRATE (16.5 mg in 1 mL) (UNII: 1Q73Q2JULR), BENZYL ALCOHOL (10.42 mg in 1 mL) (UNII: LKG8 49 4WBH), WATER (UNII: 059QF0KO0R), SODIUM HYDROXIDE (UNII: 55X04QC32I), CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)
76420-810	Mardex 25 Kit	KIT	EPIDURAL; INFILTRATION; INTRAMUSCULAR;		Asclemed USA, Inc.	10	mg/mL	Sodium Citrate (UNII: 1Q73Q2JULR), Citric Acid Monohydrate (UNII: 2968PHW8QP), Sodium Hydroxide (UNII: 55X04QC32I)

Product NDC (USA)	Proprietary Name	Dosage Form Name	Route Name	Application Number	Labeler Name	Strength	Unit	Excipients
			INTRAVENOUS; TOPICAL					
70112-555	TopiDex	KIT	INTRAMUSCULAR; INTRAVENOUS	ANDA 040491	Topicare Management, LLC	10	mg/mL	SODIUM HYDROXIDE (UNII: 55X04QC32I), SODIUM CITRATE (24.5 mg in 1 mL) (UNII: 1Q73Q2JULR), CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)
withdrawn 0006-7646-03	DECADRON Phosphate injection	INJECTION, SOLUTION	INTRAVENOUS		Merck	24	mg/ml	8 mg/ml creatinine, 10 mg/ml sodium citrate, 0.5 mg/ml disodium edetate, sodium hydroxide to adjust pH, and Water for Injection q.s., with 1 mg/ml sodium bisulfite, 1.5 mg/ml methylparaben, and 0.2 mg/ml propylparaben added as preservatives.

TABLE C: Examples of Dexamethasone Sodium Phosphate formulations (U.S. veterinary market) – Products for veterinary market

NDC or drug code	Active ingredient	Brand Name	Excipients	Concen-tration	Vial	Total Amount
0061-0884-01	Dexamethasone	Azium	Per ml: 500 mg polyethylene glycol 400, 9 mg benzyl alcohol, 1.8 mg methylparaben and 0.2 mg propylparaben as preservatives, 4.75% alcohol, HCl to adjust pH to approximately 4.9, and water for injection q.s.	2 mg/ml dexamethasone	100 mL	200 mg dexamethasone
2314118	Dexamethasone sodium phosphate	Dexacort 5	1 mg/ml methylparahydroxybenzoate, 0.1 mg/ml propylparahydroxybenzoate	5 mg/ml	100 ml	500 mg
ACVM A001421	Dexamethasone sodium phosphate	Dexadreson	15.6 mg/mL benzyl alcohol	2 mg/mL	50 ml	100 mg
11695-4017	Dexamethasone	Dexaject	Per ml: 500 mg polyethylene glycol 400, 9 mg benzyl alcohol, 1.8 mg methylparaben and 0.2 mg propylparaben as preservatives, 4.75% alcohol, HCl to adjust pH to approximately 4.9, water for injection q.s.	2 mg/mL	100 mL	200 mg
11695-4013	Dexamethasone sodium phosphate	Dexaject SP	Per ml: Sodium Citrate 10mg, Sodium Bisulfite 2mg, Benzyl Alcohol 1.5% as preservative, in Water for Injection q.s. Sodium Hydroxide and /or Hydrochloric Acid to adjust pH to between 7.0 and 8.5.	4 mg/mL DSP	100 mL	400 mg
50989-074-12	dexamethasone	Dexamethasone (Vedco, Inc)	Per ml: 500 mg polyethylene glycol 400, 9 mg benzyl alcohol, 1.8 mg methylparaben and 0.2 mg propylparaben as preservatives, 4.75% alcohol, HCl and/or NaOH to adjust pH to approximately 4.9, water for injection q.s.	2 mg/mL	100 mL	200 mg
57561-953	dexamethasone	Dexamethasone (Agri Laboratories, Ltd.)	Per ml: 500 mg polyethylene glycol 400, 9 mg benzyl alcohol, 1.8 mg methylparaben and 0.2 mg propylparaben as preservatives, 1.75% alcohol, HCl to adjust pH to approximately 4.9, water for injection q.s.	2 mg/mL	100 mL	200 mg

NDC or drug code	Active ingredient	Brand Name	Excipients	Concen-tration	Vial	Total Amount
57319-560-05	Dexamethasone	Dexamethasone (Phoenix Pharmaceuticals)	Per ml: 500 mg polyethylene glycol 400, 9 mg benzyl alcohol, 1.8 mg methylparaben and 0.2 mg propylparaben as preservatives, 4.75% alcohol, HCl to adjust pH to approximately 4.9, water for injection q.s.	2 mg/mL	100 mL	200 mg
57561-953-04	Dexamethasone	Dexamethasone injection (Agrilabs)	polyethylene glycol 400, Benzyl alcohol, Methylparaben and propylparaben.	2 mg/ml	100 mL	200 mg
49884-084-01	Dexamethasone	Dexamethasone injection (Vettek)	Per ml: 500 mg polyethylene glycol 400; 9 mg benzyl alcohol, 1.8 mg methylparaben, and 0.2 mg propylparaben as preservatives; 4.75% alcohol; HCl to adjust pH to approximately 4.9; water for injection qs.	2 mg/mL	100 mL	200 mg
54925-067-10	Dexamethasone	Dexamethasone Solution	Per ml: 500 mg polyethylene glycol 400, 9 mg benzyl alcohol, 1.8 mg methylparaben and 0.2 mg propylparaben as preservatives, 4.75% alcohol, HCl and/or sodium hydroxide to adjust pH to approximately 4.9, Water for Injection q.s.	2 mg/mL	100 mL	200 mg
13985-043-29	Dexamethasone sodium phosphate	Dexamethasone SP	Per ml: Sodium Citrate 10mg, Sodium Bisulfite 2 mg, Benzyl Alcohol 1.5% as preservative, in Water for Injection q.s. Sodium Hydroxide and /or Hydrochloric Acid to adjust pH to between 7.0 and 8.5.	4 mg/mL DSP	100 mL	400 mg
61133-0899-9	dexamethasone	Dexium	Per ml: 500 mg polyethylene glycol 400, 9 mg benzyl alcohol, 1.8 mg methylparaben and 0.2 mg propylparaben as preservatives, 4.75% alcohol, HCl to adjust pH to approximately 4.9, water for injection q.s.	2 mg/ml dexamethasone	100 mL	200 mg
	Dexamethasone	Dexa-ject	15 mg/ml Benzyl Alcohol	2 mg/mL	50 or 100 ml	100 or 200 mg

NDC or drug code	Active ingredient	Brand Name	Excipients	Concen-tration	Vial	Total Amount
11695-4013-1	Dexamethasone Sodium Phosphate	DEXAJECT SP	Per ml: Sodium Citrate 10 mg, Sodium Bisulfite 2 mg, Benzyl Alcohol 1.5% as preservative, in Water for Injection q.s. Sodium Hydroxide and /or Hydrochloric Acid to adjust pH to between 7.0 and 8.5.	4 mg/mL	100 mL	400 mg
2/5/412/2006	Dexamethasone Sodium phosphate	Dexafort Ject	Not disclosed	5 mg/ml	100 mL	500 mg
13985-533-25, 13985-533-03	Dexamethasone	Dexamethasone (Vet One)	Per ml: 500 mg polyethylene glycol 400, 9 mg benzyl alcohol, 1.8 mg methylparaben and 0.2 mg propylparaben, 4.75% alcohol, HCl to adjust pH to approximately 4.9, water for injection q.s.	2 mg/ml	100 ml	200 mg
50989-437-12	Dexamethasone	Dexamethasone (Vedco, Inc)	Per ml: 500 mg polyethylene glycol 400, 9 mg benzyl alcohol, 1.8 mg methylparaben and 0.2 mg propylparaben, 4.75% alcohol, HCl to adjust pH to approximately 4.9, water for injection q.s.	2 mg/ ml	100 ml	200 mg
17033-207-76	Per ml: 40 mg thiabendazole, 1 mg dexamethasone, 3.2 mg neomycin (from neomycin sulfate)	ThiDexaVet	glycerin, propylene glycol, purified water, hypophosphorous acid, calcium hypophosphite; about 8.5% ethyl alcohol and about 0.5% benzyl alcohol.	1 mg/ml	7.5 ml	7.5 mg

TABLE D: Examples of high dose Dexamethasone Sodium Phosphate formulations (international market)

High concentration dexamethasone sodium phosphate approved products

Compound	Brand	Strength (mg/ml)	Vial Size	Actives per ml	Inactives per ml	Preservatives per ml	Notes	Approved & Registered Markets
Dexamethasone Sodium Phosphate NDC 0006-7646-03	Decadron (Merck)	24	5 ml (120 mg)	20 mg Dexamethasone (100 mg)	10 mg sodium citrate 0.5 mg disodium edetate sodium hydroxide to adjust pH water for injection q.s.	1 mg sodium bisulfite 1.5 mg methylparaben 0.2 mg propylparaben 8 mg creatinine	**NOT AVAILABLE.** For intravenous injection only. DECADRON Phosphate injection can be given directly from the vial, or it can be added to Sodium Chloride Injection or Dextrose Injection and administered by intravenous drip. Solutions used for intravenous administration or further dilution of this product should be preservative-free when used in the neonate, especially the premature infant. When it is mixed with an infusion solution, sterile precautions should be observed. Since infusion solutions generally do not contain preservatives, mixtures should be used within 24 hours. Parenteral drug products	1. USA 2. UK 3. Ireland

Compound	Brand	Strength (mg/ml)	Vial Size	Actives per ml	Inactives per ml	Preservatives per ml	Notes	Approved & Registered Markets
							should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.	
Dexamethasone Sodium Phosphate NDC N/A	DBL™ Dexamethasone (Hospira)	24	5 ml (120 mg)	20 mg Dexamethasone (100 mg)	10 mg sodium citrate 0.5 mg disodium edetate sodium hydroxide to adjust pH water for injection q.s.	8 mg creatinine	**NOT AVAILABLE.** The intravenous and intramuscular routes of administration of DBL™ Dexamethasone Sodium Phosphate Injection should only be used where acute illness or life-threatening situations exist. Oral therapy should be substituted as soon as possible.	1. Australia 2. New Zealand (active) 3. Ireland 4. United Kingdom
Dexamethasone Sodium Phosphate NDC 63323-516-10	Fresenius Kabi APP Pharma	10	10 ml (100 mg)	8.30 mg Dexamethasone (82.5 mg)	13.5 mg sodium citrate, dihydrate; and Water for Injection, q.s. pH adjusted with citric acid or sodium hydroxide, if necessary. pH: 7.0 to 8.5.	10 mg Benzyl alcohol	**AVAILABLE**	

Compound	Brand	Strength (mg/ml)	Vial Size	Actives per ml	Inactives per ml	Preservatives per ml	Notes	Approved & Registered Markets
Dexamethasone Sodium Phosphate NDC 0069-4541-02	Pfizer	10	10 ml (100 mg)	Dexamethasone sodium phosphate 11 mg (equivalent to dexamethasone phosphate 10 mg).	Edetate Disodium 0.11 mg; Sodium Citrate Anhydrous 10 mg; Citric Acid and/or Sodium Hydroxide q.s to adjust pH 7.0 to 8.5 and Water for Injection q.s to 1 mL	Methylparaben 1.5 mg; Propylparaben 0.2 mg	**AVAILABLE**	
Dexamethasone Sodium Phosphate NDC 22000AMX00346000	Solcort™ Injection 100 mg Fuji Pharm (Shelf life: 3 years)	24	5 ml (120 mg)	20 mg Dexamethasone (100 mg)	Per 5 ml: Citric acid monohydrate 100 mg pH adjustment agent (Appropriate amount)	Benzethonium chloride 0.5 mg/5 ml	**AVAILABLE**	1. Japan Restricted to treatment of shock: hemorrhagic shock, traumatic shock emergencies, and peri-operative and post-operative shock.

TABLE E: Examples of patents disclosing Dexamethasone formulations with a much higher sulfite or excipient content

Patent	Title	Composition					Stability	Comparison to AVM0703
WO 2017/097432 A1	Preservative free pharmaceutical composition for ophthalmic administration containing dexamethasone	Dexamethasone phosphate	1.000	1.000	1.000	1.000	The final product was stored at 0, 1, 3, 6 and 9 months under long term (25°C / 60% RH) and accelerated storage conditions (40°C / 75% RH), which did not significantly change the realted substances profile conforming to the specification limits.	1/24 of DSP concentration; 2x Disodium EDTA concentration
		Dexamethasone sodium phosphate	1.093	1.093	1.093	1.093		
		Disodium EDTA	1.000	1.000	1.000	1.000		
		Sodium chloride	7.500	6.920	7.600	6.600		
		Disodium phosphate dodecahydrate	4.500	6.000	6.000	7.450		
		NaOH/HCl 0.1/1N	q.s. to 7.6					
		Total solution volume (ml)	1,00					
CN 107375200 A	Dexamethasone sodium phosphate injection and preparing method thereof	Sodium hydrogen sulfite (g)	0.4				Stored for more than 2 years, no precipitates precipitated in the life of the product (at 50°C)	Together: 2000 ppm sulfite present (AVM0703 only 35 ppm) = 57x more than AVM0703; 30 minutes (steam sterilized); AVM0703: aseptic manufacture
		Anhydrous sulfite (g)	1.6					
		Dexamethasone sodium phosphate (g)	1					
		Propylene glycol (ml)	250					
		NaOH 1N	pH 7.5-8.0					
		Water for injection (ml)	1000					
CN 101623291 A	Dexamethasone sodium phosphate injection	Dexamethasone sodium phosphate	0.1 to 1%				Only 3 months stability (at 60°C / 75% RH)	As antioxidant, sodium bisulfite, sodium sulfite, A-tocopherol, sodium metabisulfite, and sodium thiosulfate in one or more of 0.05% - 0.2% (14.7x more
		Pharmaceutically acceptable glycol (medicinal	0 to 2%					

Patent	Title	Composition		Stability	Comparison to AVM0703
		propylene glycol)			than AVM0703; sodium sulfite content of only 0.0034%)
		Sodium dihydrogen phosphate: disodium hydrogen phosphate	0.01 to 0.1 percent of mixed phosphate buffer according to ratio of 0-1:10		
		Water for injection			
		Example 5			
		Dexamethasone sodium phosphate (g)	5		
		Disodium hydrogen phosphate (g)	0.5		
		Medicinal propylene glycol (g)	10		
			Adjusted to pH 8.0, filtered, dispensed, sterilized to give injections per ml solution of dexamethasone sodium phosphate 5 mg		
		Water for injection (ml)	1000		
EP 2735305 A1	Stabilised liquid pharmaceutical preparations	INGREDIENTS: FORMULATION A (according to the invention); oral drops	Quantity for 1ml:	36 months under if stored at room temperature (25°C 62°C / 65% RH 65%) an	Use of cyclodextrins is limited by cost and toxicity at high doses. Likewise for propylene glycol: dose limiting, especially for pediatric use!
		Dexamethasone sodium phosphate	2.00 mg		
		Sodium benzoate	1.50 mg		

Patent	Title	Composition			Stability	Comparison to AVM0703
		Propylene glycol		700.00 mg		
		Sodium dihydrogen Phosphate dihydrate		5.50 mg		
		Saccharin sodium		2.00 mg		
		Hydroxypropylbetadex		6.50 mg		
		Disodium edetate		1.00 mg		
		Sodium hydroxide		0.6667 mg		
		Purified water		q.s. to 1.00 ml (328 mg)		
		EXAMPLE 4				
		[0068]				
		Preparation of an aqueous solution for injectable liquids				
		Components	Unit	Per 100ml		
		Dexamethasone sodium phosphate	mg	200		
		Propylene glycol	g	10		
		Hydroxypropyl beta cyclodextrin	g	0.65		
		Sodium dihydrogen phosphate dihydrate		q.s. for pH 7.0-8.0		
		Sodium hydroxide		q.s. for pH 7.0-8.0		
		Purified watwer		q.s. for 100 ml		

TABLE F: Examples of Dexamethasone formulations including their shelf-life as disclosed by the manufacturers in comparison with the AVM0703 F10 formulation

Name	Drug Code	Active Pharmaceu-tical Ingredient	Form and Administration	Company	Strength	Use	Composition	Volume	Shelf-life	Compar-ison
AVM0703 (F10)		Dexamethasone Sodium Phosphate	INJECTION, SOLUTION, Oral Administration	AVM Biotechnology	24 mg/ml	Human Use	Sodium Citrate (10 mg in 1 ml); Disodium Edetate (0.5 mg in 1 ml); Sodium Hydroxide (pH adjustment to 7.6)	50 ml (Target fill: 51.0 ml; nominal fill 50.0 ml)	29 - 48 months	highest strength, volume and longest shelf-life, no preservatives
Dexamethasone Sodium Phosphate	63323-506-01	Dexamethasone Sodium Phosphate	INJECTION, SOLUTION	Fresenius Kabi USA, LLC	10 mg/ml	Human Use	Sodium Citrate (24.75 mg in 1 mL); Sodium Hydroxide, Citric Acid Monohydrate	1 ml	24 months	low strength, very low volume
Dexamethasone	PL 04515/0020	Dexamethasone Sodium Phosphate	Injection	Hospira	4 mg/ml	Human Use	10 mg/ml Sodium citrate, 0.5 mg/ml disodium edetate, 0.07 mg/ml sodium sulphite anhydrous (E221), Water for Injections, sodium hydroxide and hydrochloric acid.	2 ml	18 months	70 ppm sulfite present
Dexa-ject		Dexamethasone Sodium Phosphate	Injection	Dopharma	2 mg/ mL	Animal Use	15 mg/ml Benzyl Alcohol	100 ml	18 months	benzyl alcohol present

REFERENCES

A number of publications are cited above in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below:

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STATEMENTS OF INVENTION

101. A pharmaceutical composition comprising (i) a glucocorticoid, packaged with a headspace (volume; [ml]) to glucocorticoid (weight [mg]) ratio of 0 – 0.00588, and (ii) a preservative in a concentration of less than 70 ppm.

102. The pharmaceutical composition of statement 101, wherein the glucocorticoid is dexamethasone.

103. The pharmaceutical composition of statement 101, wherein the preservative is a sulfite.

104. The pharmaceutical composition of statement 103, wherein the sulfite is sodium sulfite.

105. The pharmaceutical composition of statement 101, wherein the concentration of the preservative is 0 ppm.

106. The pharmaceutical composition of statement 101 further comprising a chelating agent.

107. The pharmaceutical composition of statment 106, wherein the chelating agent is disodium edetate.

108. The pharmaceutical composition of statement 101, wherein the concentration of the chelating agent disodium edetate is 0 ppm.

109. A method for producing a pharmaceutical composition having a low concentration of preservative, based on packing of said pharmaceutical composition with a headspace (volume; [ml]) to glucocorticoid (weight [mg]) ratio of 0 – 0.00588.

110. The method of statement 109, wherein the preservative is a sulfite.

111. The method of statement 109, wherein the sulfite is sodium sulfite.

112. The method of statement 109, wherein the concentration of the preservative is 0 ppm.

113. The method of statement 109, further comprising a chelating agent.

114. The method of statement 109, further comprising disodium edetate as chelating agent.

115. The method of statement 109, wherein the concentration of the chelating agent disodium edetate is 0 ppm.

116. A method of treating a host in need of glucocorticoid treatment, comprising administering the pharmaceutical compositon of claim statement 101.

117. The method of statement 116, wherein the glucocorticoid is dexamethasone.

118. The method of statement 116, wherein the headspace to glucocorticoid is 0 – 0.00588.

119. The method of statement 116, wherein the preservative is a sulfite.

120. The method of statement 116, wherein the sulfite is sodium sulfite.

121. The method of statement 116, wherein the concentration of the preservative is 0 ppm.

122. The method of statement 116, further comprising a chelating agent.

123. The method of statement 116, further comprising disodium edetate as chelating agent.

124. The method of statement 116, wherein the concentration of the chelating agent disodium edetate is 0 ppm.

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201. An aqueous pharmaceutical formulation comprising a glucocorticoid, wherein the formulation is packaged in a container with a headspace volume (ml) to total glucocorticoid content (mg) ratio of 0.007 or less.

Headspace to API ratio

202. The aqueous pharmaceutical formulation of statement 201, wherein the headspace volume (ml) to total glucocorticoid content (mg) ratio is 0.0065 or less, 0.0060 or less, 0.00588 or less, 0.0055 or less, 0.0050 or less, 0.0045 or less, 0.0040 or less, 0.0035 or less, 0.0030 or less, 0.0025 or less, 0.0020 or less, 0.0015 or less, or 0.0010 or less.

203. The aqueous pharmaceutical formulation of statement 202, wherein the headspace volume (ml) to total glucocorticoid content (mg) ratio is 0.00588 or less.

Sulfite to API ratio

204. The aqueous pharmaceutical formulation of any one of statements 201 to 203, wherein the formulation is packaged in a container with a total sulfite content (mg) to total glucocorticoid content (mg) ratio of 0.0040 or less, 0.0035 or less, 0.0030 or less, 0.0025 or less, 0.0020 or less, 0.0015 or less, 0.00146 or less, or 0.0010 or less.

205. The aqueous pharmaceutical formulation of statement 204, wherein the formulation is packaged in a container with a total sulfite content (mg) to total glucocorticoid content (mg) ratio of 0.00150 or less, preferably 0.00146 or less.

Headspace volume

206. The aqueous pharmaceutical formulation of any one of statements 201 to 205, wherein the headspace volume is or is less than about 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 ml.

207. The aqueous pharmaceutical formulation of statement 206, wherein the headspace volume is or is less than about 8 ml.

Headspace oxygen

208. The aqueous pharmaceutical formulation of any one of statements 201 to 207, wherein the headspace volume comprises less than about 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 % oxygen.

209. The aqueous pharmaceutical formulation of statement 208, wherein the headspace volume comprises less than about 5% oxygen.

210. The aqueous pharmaceutical formulation of any one of statements 201 to 207, wherein the headspace volume comprises 0 % oxygen.

Preservative concentration

211. The aqueous pharmaceutical formulation of any one of statements 201 to 210, wherein the formulation comprises one or more preservative, wherein the concentration of preservatives is or is less than about 0.1 mg/ml.

212. The aqueous pharmaceutical formulation of statement 211, wherein the concentration of preservatives is or is less than about 0.09 mg/ml, is or is less than about 0.08 mg/ml, is or is less than about 0.07 mg/ml, is or is less than about 0.06 mg/ml, is or is less than about 0.05 mg/ml, is or is less than about 0.04 mg/ml, is or is less than about 0.035 mg/ml, is or is less than about 0.03 mg/ml, is or is less than about 0.02 mg/ml, or is or is less than about 0.01 mg/ml.

213. The aqueous pharmaceutical formulation of statement 212, wherein the concentration of preservatives is or is less than about 0.07 mg/ml, preferably wherein the concentration of preservatives is or is less than about 0.035 mg/ml.

214. The aqueous pharmaceutical formulation of any one of statements 201 to 210, wherein the concentration of preservative is 0 mg/ml.

215. The aqueous pharmaceutical formulation of any one of statements 201 to 210, wherein the formulation does not comprise a preservative.

Preservative identity

216. The aqueous pharmaceutical formulation of any one of statements 211 to 215, wherein the preservative is a sulfite, a paraben, benzyl alcohol, benzethonium chloride, propylene glycol, and / or creatinine.

217. The aqueous pharmaceutical formulation of statement 216, wherein the sulfite is sodium sulfite (anhydrous), sodium bisulfite, and / or sodium metabisulfite.

218. The aqueous pharmaceutical formulation of statement 216, wherein the paraben is methylparaben, propylparaben, ethylparaben, butylparaben, isopropylparaben and / or isobutylparaben, preferably wherein the paraben is methylparaben and / or propylparaben.

Chelating agent concentration

219. The aqueous pharmaceutical formulation of any one of statements 201 to 219, wherein the formulation comprises one or more chelating agent, wherein the concentration of chelating agent is or is less than about 0.50 mg/ml.

220. The aqueous pharmaceutical formulation of statement 219, wherein the concentration of chelating agent is or is less than about 0.45 mg/ml, is or is less than about 0.40 mg/ml, is or is less than about 0.35 mg/ml, is or is less than about 0.30 mg/ml, is or is less than about 0.25 mg/ml, is or is less than about 0.20 mg/ml, is or is less than about 0.15 mg/ml, is or is less than about 0.10 mg/ml, is or is less than about 0.10 mg/ml, or is or is less than about 0.05 mg/ml.

221. The aqueous pharmaceutical formulation of any one of statements 201 to 219, wherein the concentration of chelating agent is 0 mg/ml.

222. The aqueous pharmaceutical formulation of any one of statements 201 to 219, wherein the formulation does not comprise a chelating agent.

Chelating agent identity

223. The aqueous pharmaceutical formulation of any one of statements 201 to 222, wherein the chelating agent is ethylenediaminetetraacetic acid (EDTA), sodium edetate, disodium edetate, tetrasodium edetate, calcium disodium edetate, calcium versetamide sodium, calteridol, and / or diethylenetriaminepenta acetic acid (DPTA).

224. The aqueous pharmaceutical formulation of statement 223, wherein the chelating agent is disodium edetate (disodium EDTA).

Glucocorticoid identity

225. The aqueous pharmaceutical formulation of any one of statements 201 to 224, wherein the glucocorticoid is selected from the group consisting of dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, prednylidene, cortisone, budesonide, betamethasone and beclomethasone.

226. The aqueous pharmaceutical formulation of statement 225,.wherein the glucocorticoid comprises dexamethasone, optionally wherein the dexamethasone is selected from the group consisting of dexamethasone base, dexamethasone sodium phosphate, dexamethasone hemisuccinate, dexamethasone sodium succinate, dexamethasone succinate, and dexamethasone acetate.

227. The aqueous pharmaceutical formulation of statement 226, wherein the dexamethasone is dexamethasone sodium phosphate.

Glucocorticoid concentration

228. The aqueous pharmaceutical formulation of any one of statements 201 to 227, wherein the concentration of glucocorticoid is or is at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, or 45 mg/ml.

229. The aqueous pharmaceutical formulation of statement 228, wherein the concentration of glucocorticoid is or is at least about 24 mg/ml.

230. The aqueous pharmaceutical formulation of statement 228, wherein the concentration of glucocorticoid is or is at least about 30 mg/ml.

231. The aqueous pharmaceutical formulation of statement 228, wherein the concentration of glucocorticoid is or is at least about 45 mg/ml.

Formulation pH

232. The aqueous pharmaceutical formulation of any one of statements 201 to 231, wherein the pH of the formulation is about 7.0 to about 8.2, about 7.2 to about 8.0, about 7.3 to about 7.9, or about 7.4 to about 7.8

233. The aqueous pharmaceutical formulation of statement 232, wherein the pH of the formulation is about 7.4 to about 7.8, preferably wherein the pH of the formulation is about 7.6.

Other components of formulation

234. The aqueous pharmaceutical formulation of any one of statements 201 to 233, wherein the formulation comprises a buffer.

235. The aqueous pharmaceutical formulation of statement 234, wherein the buffer is sodium citrate.

236. The aqueous pharmaceutical formulation of statement 234 or 235, wherein the concentration of buffer is about 10 mg/ml.

Container type & volume

237. The aqueous pharmaceutical formulation of any one of statements 201 to 236, wherein the container is a vial, ampoule, solvent reservoir, storage bottle, medical bottle, syringe, or bottle, preferably wherein the container is a vial, ampoule, or bottle.

238. The aqueous pharmaceutical formulation of any one of statements 201 to 237, wherein the volume of the container is or is at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 51, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 ml.

239. The aqueous pharmaceutical formulation of statement 238, wherein the volume of the container is or is at least about 51 ml.

240. The aqueous pharmaceutical formulation of any one of statements 201 to 239, wherein the volume of glucocorticoid packaged in the container is at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 ml.

Functional features

241. The aqueous pharmaceutical formulation of any one of statements 201 to 240, wherein the shelf-life of the formulation is at least about 18, 24, 36, or 48 months when stored between 20°C to 40°C or between 15°C to 20°C.

242. The aqueous pharmaceutical formulation of any one of statements 201 to 240, wherein the formulation remains stable when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

243. The aqueous pharmaceutical formulation of any one of statements 201 to 242, wherein the formulation exhibits less than about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2, 3.4, 3.6, 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, 5.0 % degradation of the glucocorticoid when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

244. The aqueous pharmaceutical formulation of any one of statements 201 to 242, wherein the the amount of glucocorticoid in the formulation is maintained above about 95.0, 95.2, 95.4, 95.6, 96.0, 96.2, 96.4, 96.6, 96.8, 97.0, 97.2, 97.4, 97.6, 98.0, 98.2, 98.4, 98.6, 98.8, 99.0, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, or 99.9 % as compared to the date of manufacture when the formulation is stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

245. The aqueous pharmaceutical formulation of any one of statements 201 to 242, wherein the the amount of glucocorticoid in the formulation is maintained between ± 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2, 3.4, 3.6, 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, or 5.0 % as compared to the date of manufacture when the formulation is stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

246. The aqueous pharmaceutical formulation of any one of statements 201 to 245, wherein the formulation exhibits less than ± 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.2, 1.4, 1.6, 1.8, or 2.0 change in pH when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

247. The aqueous pharmaceutical formulation of any one of statements 201 to 246, wherein the glucocorticoid is dexamethasone sodium phosphate, and

wherein the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity A when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

248. The aqueous pharmaceutical formulation of any one of statements 201 to 247, wherein the glucocorticoid is dexamethasone sodium phosphate, and

wherein the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity B when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

249. The aqueous pharmaceutical formulation of any one of statements 201 to 248, wherein the glucocorticoid is dexamethasone sodium phosphate, and

wherein the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity C when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

250. The aqueous pharmaceutical formulation of any one of statements 201 to 249, wherein the glucocorticoid is dexamethasone sodium phosphate, and

wherein the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity D when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

251. The aqueous pharmaceutical formulation of any one of statements 201 to 250, wherein the glucocorticoid is dexamethasone sodium phosphate, and

wherein the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity E when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

252. The aqueous pharmaceutical formulation of any one of statements 201 to 251, wherein the glucocorticoid is dexamethasone sodium phosphate, and

wherein the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity F when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

253. The aqueous pharmaceutical formulation of any one of statements 201 to 252, wherein the glucocorticoid is dexamethasone sodium phosphate, and

wherein the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity G when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

254. The aqueous pharmaceutical formulation of any one of statements 201 to 253, wherein the formulation exhibits less than about 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19 0.20, 0.21, 0.22, 0.23, 0.24, 0.25, 0.26, 0.27, 0.28, 0.29, or 0.30 % accumulation of unspecified impurities when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

255. The aqueous pharmaceutical formulation of any one of statements 201 to 254, wherein the formulation exhibits less than about 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2, 3.4, 3.6, 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, or 5.0 % accumulation of total impurities when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

Medical use

256. The aqueous pharmaceutical formulation of any one of statements 201 to 255, for use in a method of treatment.

257. Use of the aqueous pharmaceutical formulation of any one of statements 201 to 255 for the preparation of a medicament for use in a method of treatment.

258. A method of treatment comprising administering to a subject in need thereof, a therapeutically effective amount of the aqueous pharmaceutical formulation of any one of statements 201 to 255.

259. The formulation for use, use, or method of any one of statements 256 to 258, wherein the method is a method of reducing stem cell accumulation in the spleen in a subject, the method comprising administering the formulation to the subject prior to stem cell treatment.

260. The formulation for use, use, or method of any one of statements 256 to 258, wherein the method is a method of enhancing adoptive cellular therapy (ACT) in a subject, the method comprising administering the formulation to the subject prior to adoptive cellular therapy.

261. The formulation for use, use, or method of any one of statements 256 to 258, wherein the method is a method of treatment of a lymphocyte mediated disease in a subject, the method comprising administering the formulation to the subject.

Method of manufacture

262. A method for stabilising an aqueous pharmaceutical formulation comprising a glucocorticoid, the method comprising packaging the aqueous pharmaceutical formulation of any one of statements 201 to 255 into a container with a headspace volume (ml) to total glucocorticoid content (mg) ratio of 0.007 or less.

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301. An aqueous pharmaceutical formulation comprising a glucocorticoid and a preservative, wherein the concentration of glucocorticoid is at least about 24 mg/ml, and the concentration of preservative is less than about 0.1 mg/ml.

302. An aqueous pharmaceutical formulation comprising a glucocorticoid and a preservative, wherein the concentration of glucocorticoid is at least about 24 mg/ml, and wherein the preservative comprises:

a sulfite present in a concentration of less than about 1 mg/ml;
a paraben present in a concentration of less than about 0.2 mg/ml;
creatinine present in a concentration of less than about 8 mg/ml; and/or
benzethonium chloride present in a concentration of less than about 0.1 mg/ml.

303. The aqueous pharmaceutical formulation of statement 302, wherein the concentration of preservative is less than about 0.1 mg/ml.

Headspace to API ratio

304. The aqueous pharmaceutical formulation of any one of statements 301 to 303, wherein the formulation is packaged in a container with a headspace volume (ml) to total glucocorticoid content (mg) ratio of 0.007 or less

305. The aqueous pharmaceutical formulation of statement 304, wherein the headspace volume (ml) to total glucocorticoid content (mg) ratio is 0.0065 or less, 0.0060 or less, 0.00588 or less, 0.0055 or less, 0.0050 or less, 0.0045 or less, 0.0040 or less, 0.0035 or less, 0.0030 or less, 0.0025 or less, 0.0020 or less, 0.0015 or less, or 0.0010 or less.

306. The aqueous pharmaceutical formulation of statement 305, wherein the headspace volume (ml) to total glucocorticoid content (mg) ratio is 0.00588 or less.

Sulfite to API ratio

307. The aqueous pharmaceutical formulation of any one of statements 301 to 306, wherein the formulation is packaged in a container with a total sulfite content (mg) to total glucocorticoid content (mg) ratio of 0.0040 or less, 0.0035 or less, 0.0030 or less, 0.0025 or less, 0.0020 or less, 0.0015 or less, 0.00146 or less, or 0.0010 or less.

308. The aqueous pharmaceutical formulation of statement 307, wherein the formulation is packaged in a container with a total sulfite content (mg) to total glucocorticoid content (mg) ratio of 0.00150 or less, preferably 0.00146 or less.

Headspace volume

309. The aqueous pharmaceutical formulation of any one of statements 301 to 308, wherein the headspace volume is or is less than about 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 ml.

310. The aqueous pharmaceutical formulation of statement 309, wherein the headspace volume is or is less than about 8 ml.

Headspace oxygen

311. The aqueous pharmaceutical formulation of any one of statements 301 to 310, wherein the headspace volume comprises less than about 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 % oxygen.

312. The aqueous pharmaceutical formulation of statement 311, wherein the headspace volume comprises less than about 5% oxygen.

313. The aqueous pharmaceutical formulation of any one of statements 301 to 312, wherein the headspace volume comprises 0 % oxygen.

Preservative concentration

314. The aqueous pharmaceutical formulation of any one of statements 301 to 313, wherein the concentration of preservative is or is less than about 0.09 mg/ml, is or is less than about 0.08 mg/ml, is or is less than about 0.07 mg/ml, is or is less than about 0.06 mg/ml, is or is less than about 0.05 mg/ml, is or is less than about 0.04 mg/ml, is or is less than about 0.035 mg/ml, is or is less than about 0.03 mg/ml, is or is less than about 0.02 mg/ml, or is or is less than about 0.01 mg/ml.

315. The aqueous pharmaceutical formulation of statement 314, wherein the concentration of preservative is or is less than about 0.07 mg/ml, preferably wherein the concentration of preservative is or is less than about 0.035 mg/ml.

316. The aqueous pharmaceutical formulation of any one of statements 301 to 313, wherein the concentration of preservative is 0 mg/ml.

317. The aqueous pharmaceutical formulation of any one of statements 301 to 313, wherein the formulation does not comprise a preservative.

Preservative identity

318. The aqueous pharmaceutical formulation of any one of statements 301 to 317, wherein the preservative is a sulfite, a paraben, benzyl alcohol, benzethonium chloride, propylene glycol, and / or creatinine

319. The aqueous pharmaceutical formulation of statement 318, wherein the sulfite is sodium sulfite (anhydrous), sodium bisulfite, and / or sodium metabisulfite.

320. The aqueous pharmaceutical formulation of statement 318, wherein the paraben is methylparaben, propylparaben, ethylparaben, butylparaben, isopropylparaben and / or isobutylparaben, preferably wherein the paraben is methylparaben and / or propylparaben .

Chelating agent concentration

321. The aqueous pharmaceutical formulation of any one of statements 301 to 321, wherein the formulation comprises one or more chelating agent, wherein the concentration of chelating agent is or is less than about 0.50 mg/ml.

322. The aqueous pharmaceutical formulation of statement 321, wherein the concentration of chelating agent is or is less than about 0.45 mg/ml, is or is less than about 0.40 mg/ml, is or is less than about 0.35 mg/ml, is or is less than about 0.30 mg/ml, is or is less than about 0.25 mg/ml, is or is less than about 0.20 mg/ml, is or is less than about 0.15 mg/ml, is or is less than about 0.10 mg/ml, is or is less than about 0.10 mg/ml, or is or is less than about 0.05 mg/ml.

323. The aqueous pharmaceutical formulation of any one of statements 301 to 321, wherein the concentration of chelating agent is 0 mg/ml.

324. The aqueous pharmaceutical formulation of any one of statements 301 to 321, wherein the formulation does not comprise a chelating agent.

Chelating agent identity

325. The aqueous pharmaceutical formulation of any one of statements 301 to 324, wherein the chelating agent is ethylenediaminetetraacetic acid (EDTA), sodium edetate, disodium edetate, tetrasodium edetate, calcium disodium edetate, calcium versetamide sodium, calteridol, and / or diethylenetriaminepenta acetic acid (DPTA).

326. The aqueous pharmaceutical formulation of statement 325, wherein the chelating agent is disodium edetate (disodium EDTA).

Glucocorticoid identity

327. The aqueous pharmaceutical formulation of any one of statements 301 to 326, wherein the glucocorticoid is selected from the group consisting of dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, prednylidene, cortisone, budesonide, betamethasone and beclomethasone.

328. The aqueous pharmaceutical formulation of statement 327,.wherein the glucocorticoid comprises dexamethasone, optionally wherein the dexamethasone is selected from the group consisting of dexamethasone base, dexamethasone sodium phosphate, dexamethasone hemisuccinate, dexamethasone sodium succinate, dexamethasone succinate, and dexamethasone acetate.

329. The aqueous pharmaceutical formulation of statement 328, wherein the dexamethasone is dexamethasone sodium phosphate.

Glucocorticoid concentration

330. The aqueous pharmaceutical formulation of any one of statements 301 to 329, wherein the concentration of glucocorticoid is or is at least about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, or 45 mg/ml.

331. The aqueous pharmaceutical formulation of statement 330, wherein the concentration of glucocorticoid is or is at least about 30 mg/ml.

332. The aqueous pharmaceutical formulation of statement 330, wherein the concentration of glucocorticoid is or is at least about 45 mg/ml.

Formulation pH

333. The aqueous pharmaceutical formulation of any one of statements 301 to 332, wherein the pH of the formulation is about 7.0 to about 8.2, about 7.2 to about 8.0, about 7.3 to about 7.9, or about 7.4 to about 7.8

334. The aqueous pharmaceutical formulation of statement 333, wherein the pH of the formulation is about 7.4 to about 7.8, preferably wherein the pH of the formulation is about 7.6.

Other components of formulation

335. The aqueous pharmaceutical formulation of any one of statements 301 to 334, wherein the formulation comprises a buffer.

336. The aqueous pharmaceutical formulation of statement 335, wherein the buffer is sodium citrate.

337. The aqueous pharmaceutical formulation of statement 335 or 336, wherein the concentration of buffer is about 10 mg/ml.

Container type & volume

338. The aqueous pharmaceutical formulation of any one of statements 301 to 337, wherein the container is a vial, ampoule, solvent reservoir, storage bottle, medical bottle, syringe, or bottle, preferably wherein the container is a vial, ampoule, or bottle.

339. The aqueous pharmaceutical formulation of any one of statements 301 to 338, wherein the volume of the container is or is at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 51, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 ml.

340. The aqueous pharmaceutical formulation of statement 339, wherein the volume of the container is or is at least about 51 ml.

341. The aqueous pharmaceutical formulation of any one of statements 301 to 340, wherein the volume of glucocorticoid packaged in the container is at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 ml.

Functional features

342. The aqueous pharmaceutical formulation of any one of statements 301 to 341, wherein the shelf-life of the formulation is at least about 18, 24, 36, or 48 months when stored between 20°C to 40°C or between 15°C to 20°C.

343. The aqueous pharmaceutical formulation of any one of statements 301 to 341, wherein the formulation remains stable when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

344. The aqueous pharmaceutical formulation of any one of statements 301 to 343, wherein the formulation exhibits less than about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2, 3.4, 3.6, 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, 5.0 % degradation of the glucocorticoid when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

345. The aqueous pharmaceutical formulation of any one of statements 301 to 343, wherein the the amount of glucocorticoid in the formulation is maintained above about 95.0, 95.2, 95.4, 95.6, 96.0, 96.2, 96.4, 96.6, 96.8, 97.0, 97.2, 97.4, 97.6, 98.0, 98.2, 98.4, 98.6, 98.8, 99.0, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, or 99.9 % as compared to the date of manufacture when the formulation is stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

346. The aqueous pharmaceutical formulation of any one of statements 301 to 343, wherein the the amount of glucocorticoid in the formulation is maintained between ± 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2, 3.4, 3.6, 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, or 5.0 % as compared to the date of manufacture when the formulation is stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

347. The aqueous pharmaceutical formulation of any one of statements 301 to 346, wherein the formulation exhibits less than ± 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.2,

1.4, 1.6, 1.8, or 2.0 change in pH when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

348. The aqueous pharmaceutical formulation of any one of statements 301 to 347, wherein the glucocorticoid is dexamethasone sodium phosphate, and

wherein the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity A when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

349. The aqueous pharmaceutical formulation of any one of statements 301 to 348, wherein the glucocorticoid is dexamethasone sodium phosphate, and

wherein the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity B when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

350. The aqueous pharmaceutical formulation of any one of statements 301 to 349, wherein the glucocorticoid is dexamethasone sodium phosphate, and

wherein the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity C when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

351. The aqueous pharmaceutical formulation of any one of statements 301 to 350, wherein the glucocorticoid is dexamethasone sodium phosphate, and

wherein the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity D when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

352. The aqueous pharmaceutical formulation of any one of statements 301 to 351, wherein the glucocorticoid is dexamethasone sodium phosphate, and

wherein the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity E when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

353. The aqueous pharmaceutical formulation of any one of statements 301 to 352, wherein the glucocorticoid is dexamethasone sodium phosphate, and

wherein the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity F when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

354. The aqueous pharmaceutical formulation of any one of statements 301 to 353, wherein the glucocorticoid is dexamethasone sodium phosphate, and

wherein the formulation exhibits less than about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, or 1.0 % accumulation of impurity G when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

355. The aqueous pharmaceutical formulation of any one of statements 301 to 354, wherein the formulation exhibits less than about 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19 0.20, 0.21, 0.22, 0.23, 0.24, 0.25, 0.26, 0.27, 0.28, 0.29, or 3.0 % accumulation of unspecified impurities when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

356. The aqueous pharmaceutical formulation of any one of statements 301 to 355, wherein the formulation exhibits less than about 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2, 3.4, 3.6, 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, or 5.0 % accumulation of total impurities when stored between 20°C to 40°C or between 15°C to 20°C for at least about 18, 24, 36, or 48 months.

Medical use

357. The aqueous pharmaceutical formulation of any one of statements 301 to 356, for use in a method of treatment.

358. Use of the aqueous pharmaceutical formulation of any one of statements 301 to 356 for the preparation of a medicament for use in a method of treatment.

359. A method of treatment comprising administering to a subject in need thereof, a therapeutically effective amount of the aqueous pharmaceutical formulation of any one of statements 301 to 356.

360. The formulation for use, use, or method of any one of statements 357 to 359, wherein the method is a method of reducing stem cell accumulation in the spleen in a subject, the method comprising administering the formulation to the subject prior to stem cell treatment.

361. The formulation for use, use, or method of any one of statements 357 to 359, wherein the method is a method of enhancing adoptive cellular therapy (ACT) in a subject, the method comprising administering the formulation to the subject prior to adoptive cellular therapy.

362. The formulation for use, use, or method of any one of statements 357 to 359, wherein the method is a method of treatment of a lymphocyte mediated disease in a subject, the method comprising administering the formulation to the subject.

Method of manufacture

363. A method for stabilising an aqueous pharmaceutical formulation comprising a glucocorticoid, the method comprising packaging the aqueous pharmaceutical formulation of any one of statements 301 to 356 into a container with a headspace volume (ml) to total glucocorticoid content (mg) ratio of 0.007 or less.

In this specification, the terms "comprise", "comprises", "comprising" or similar terms are intended to mean a non-exclusive inclusion, such that a system, method or apparatus that comprises a list of elements does not include those elements solely, but may well include other elements not listed.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge in Australia.

2019378874 13 May 2025

CLAIMS

1. An aqueous pharmaceutical formulation comprising dexamethasone and a concentration of equal to or less than about 0.1 mg/ml of a preservative, wherein the formulation is packaged in a container with a headspace volume (ml) to dexamethasone content (mg) ratio of 0.0065 or less.

2. The aqueous pharmaceutical formulation of claim 1, wherein the concentration of dexamethasone is at least 24 mg/ml.

3. The aqueous pharmaceutical formulation of any preceding claim, wherein the headspace volume (ml) to dexamethasone content (mg) ratio is:

(i) 0.0060 or less;

(ii) 0.00588 or less;

(iii) 0.0010 - 0.0065; or

(iv) 0.0010 - 0.0060.

4. The aqueous pharmaceutical formulation of any preceding claim, wherein the headspace volume comprises:

(i) less than about 21 % oxygen;

(ii) less than about 11 % oxygen;

(iii) less than about 10 % oxygen; or

(iv) less than about 5 % oxygen.

5. The aqueous pharmaceutical formulation of any preceding claim, wherein the concentration of preservative is or is less than about 0.035 mg/ml.

6. The aqueous pharmaceutical formulation of any preceding claim, wherein the preservative is a sulfite, a paraben, benzyl alcohol, benzethonium chloride, propylene glycol, and / or creatinine.

7. The aqueous pharmaceutical formulation of claim 7, wherein the sulfite is sodium sulfite (anhydrous), sodium bisulfite, and / or sodium metabisulfite.

8. The aqueous pharmaceutical formulation of claim 1, wherein the formulation does not comprise a preservative.

9. The aqueous pharmaceutical formulation of any preceding claim, wherein the formulation comprises one or more chelating agent, wherein the concentration of chelating agent is or is less than about 0.50 mg/ml.

10. The aqueous pharmaceutical formulation of claim 9, wherein the chelating agent is disodium edetate (disodium EDTA).

11. The aqueous pharmaceutical formulation of claim 1, wherein the formulation does not comprise a chelating agent.

12. The aqueous pharmaceutical formulation of any preceding claim, wherein the dexamethasone is selected from the group consisting of dexamethasone base, dexamethasone sodium phosphate and dexamethasone acetate.

13. The aqueous pharmaceutical formulation of claim 12, wherein the dexamethasone is dexamethasone sodium phosphate.

14. The aqueous pharmaceutical formulation of any preceding claim, wherein:

(i) the shelf-life of the formulation is at least about 18, 24, 36, or 48 months when stored between 2°C to 40°C;

(ii) the formulation remains stable when stored between 2°C to 40°C for at least about 18, 24, 36, or 48 months;

(iii) the amount of dexamethasone in the formulation is maintained between ± 5.0 % as compared to the date of manufacture when the formulation is stored between 2°C to 40°C for at least about 18, 24, 36, or 48 months;

(iv) the formulation exhibits less than ± 0.5 change in pH when stored between 2°C to 40°C for at least about 18, 24, 36, or 48 months;

(v) the formulation exhibits less than about 0.20 % accumulation of unspecified impurities when stored between 2°C to 40°C for at least about 18, 24, 36, or 48 months; and / or

(vi) the formulation exhibits less than about 3.0 % accumulation of total impurities when stored between 2°C to 40°C for at least about 18, 24, 36, or 48 months.

15. The aqueous pharmaceutical formulation of any preceding claim, wherein:
the dexamethasone is dexamethasone sodium phosphate and:

(i) the formulation exhibits less than about 0.50 % accumulation of impurity A when stored between 2°C to 40°C for at least about 18, 24, 36, or 48 months;

(ii) the formulation exhibits less than about 0.50 % accumulation of impurity B when stored between 2°C to 40°C for at least about 18, 24, 36, or 48 months;

(iii) the formulation exhibits less than about 0.50 % accumulation of impurity G when stored between 2°C to 40°C for at least about 18, 24, 36, or 48 months.

16. Use of the aqueous pharmaceutical formulation of any preceding claim for the preparation of a medicament for use in a method of treatment of a lymphocyte mediated disease, an inflammatory disease, an immunosuppressive disease, an autoimmune disease, or cancer, or use in a method of enhancing adoptive cellular therapy (ACT) in a subject.

17. A method of treatment comprising administering to a subject in need thereof, a therapeutically effective amount of the aqueous pharmaceutical formulation of any preceding claim; wherein the method of treatment is a method of treating a lymphocyte mediated disease, an inflammatory disease, an immunosuppressive disease, an autoimmune disease, or cancer, or a method of enhancing adoptive cellular therapy (ACT) in a subject.

18. A method for stabilising an aqueous pharmaceutical formulation comprising dexamethasone and a preservative, the method comprising packaging the aqueous pharmaceutical formulation of any preceding claim into a container with a headspace volume (ml) to dexamethasone content (mg) ratio of 0.0065 or less,

wherein the concentration of preservative is or is less than about 0.1 mg/ml.

19. The method of claim 18, wherein the concentration of dexamethasone is at least 24 mg/ml.

20. The method of claim 18, wherein the headspace volume comprises:

(i) less than about 21 % oxygen;

(ii) less than about 11 % oxygen;

(iii) less than about 10 % oxygen; or

(iv) less than about 5 % oxygen.

Figure 1

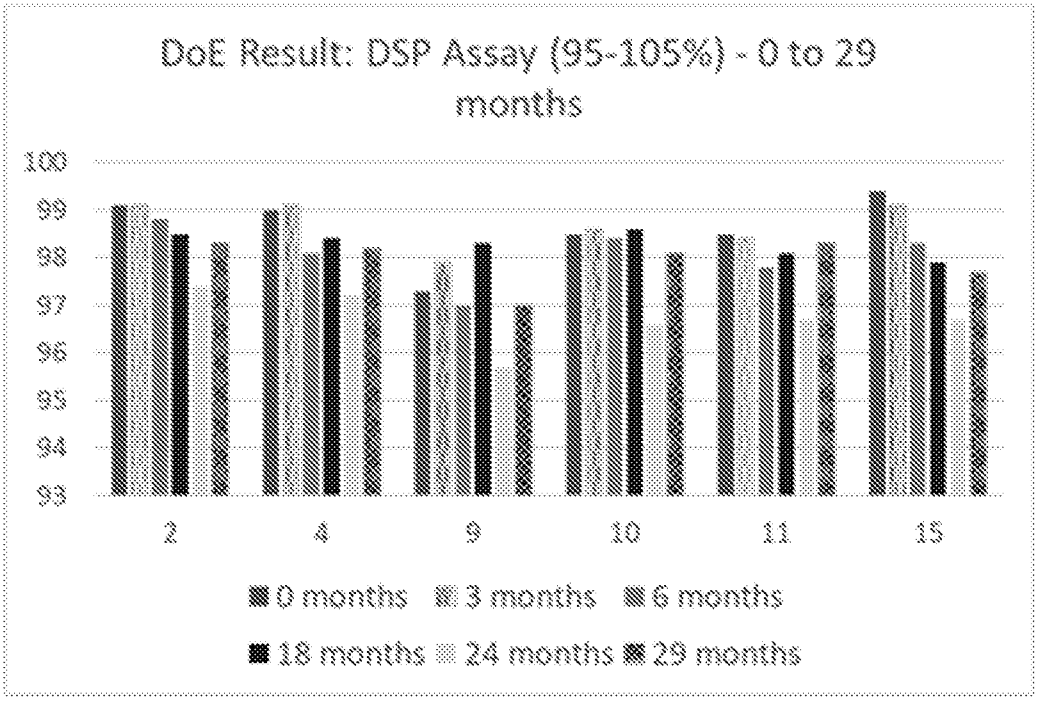


Figure 2

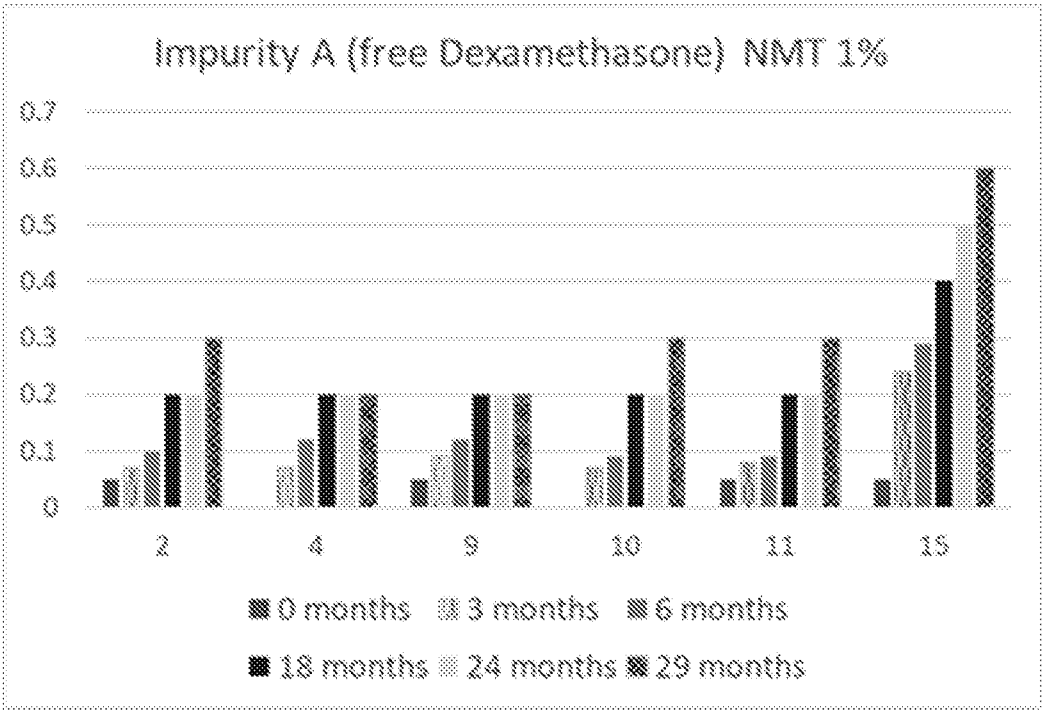


Figure 3

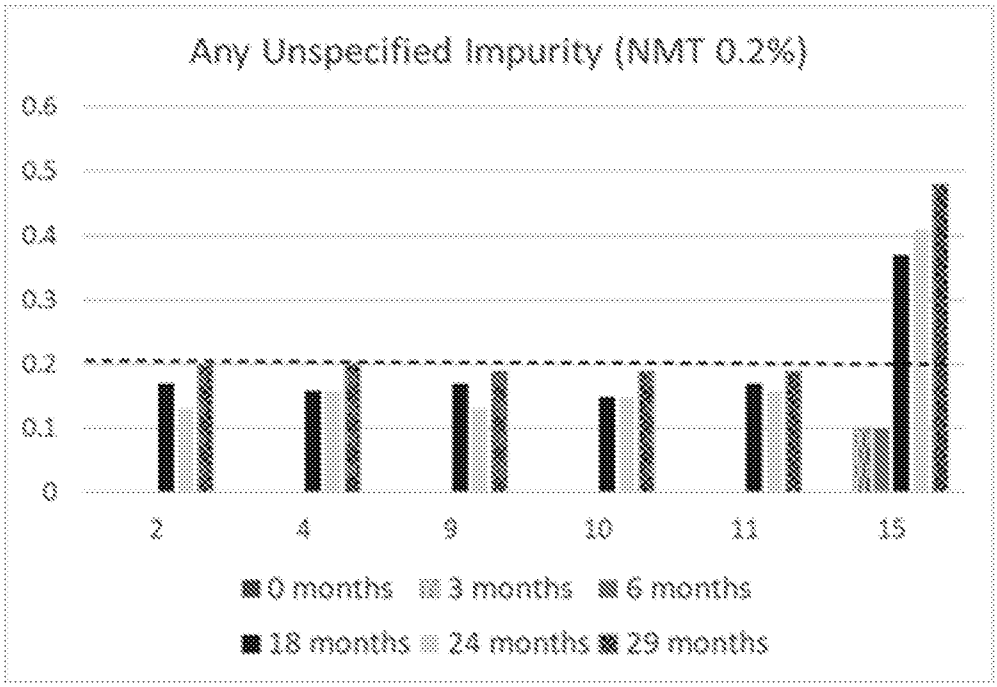


Figure 4

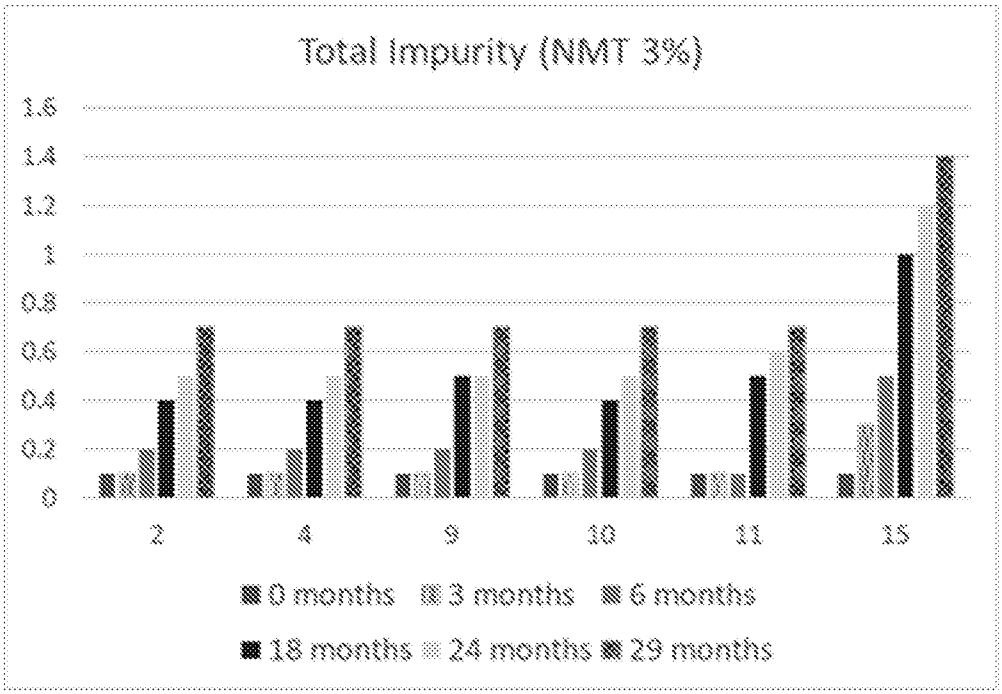
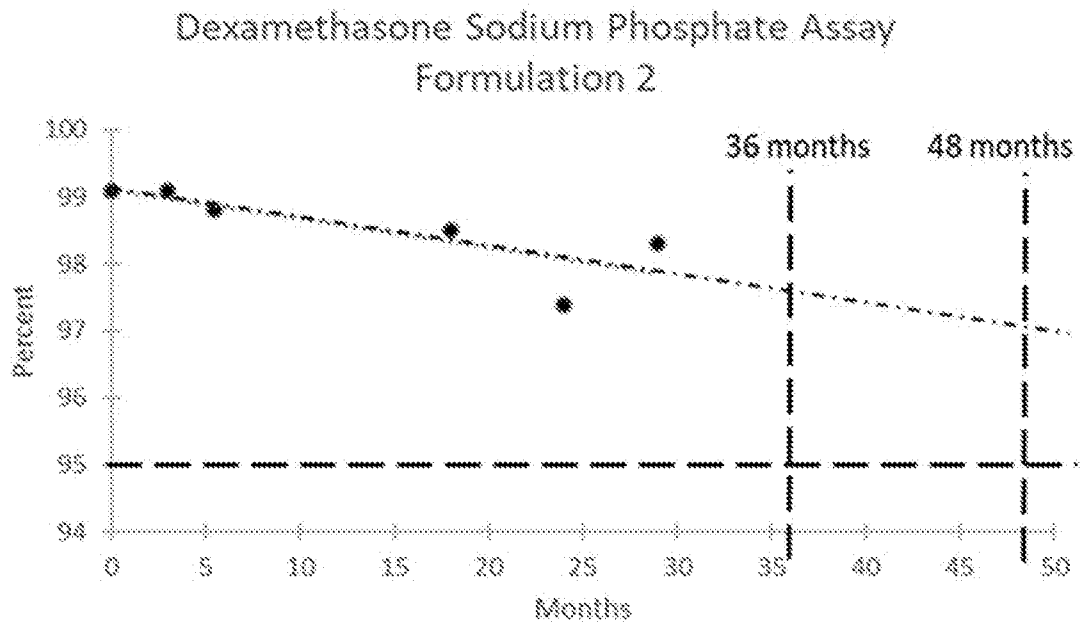


Figure 5


Dexamethasone Sodium Phosphate Assay
Formulation 2
36 months
48 months
Percent
100
99
98
97
96
95
94
0
5
10
15
20
25
30
35
40
45
50
Months

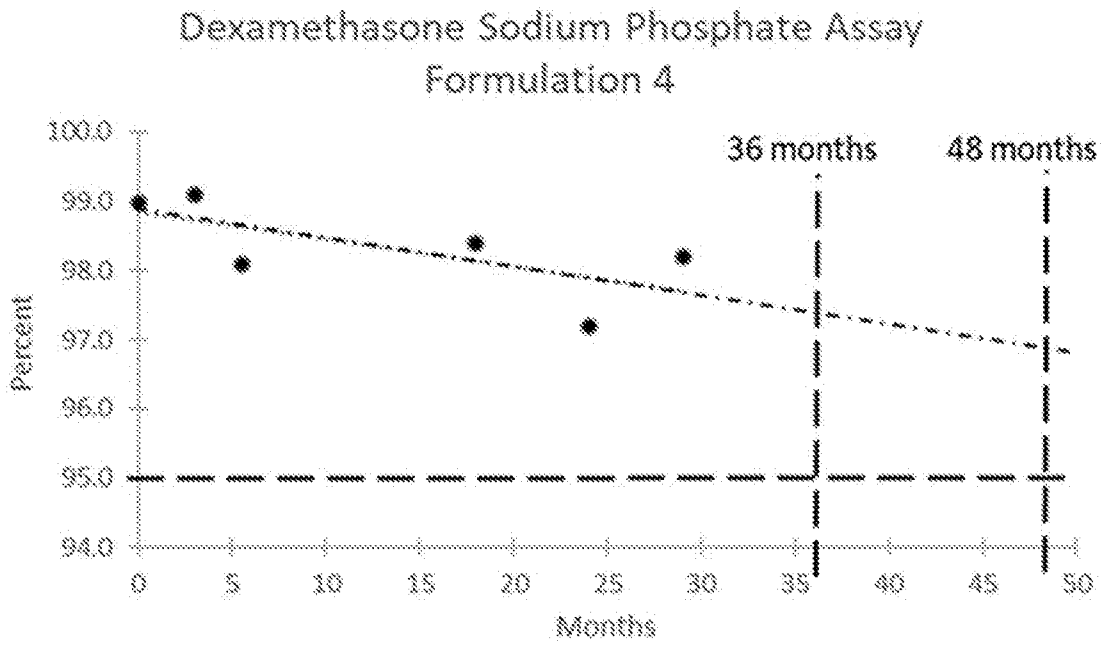

Dexamethasone Sodium Phosphate Assay
Formulation 4
36 months
48 months
Percent
100.0
99.0
98.0
97.0
96.0
95.0
94.0
0
5
10
15
20
25
30
35
40
45
50
Months

Figure 6

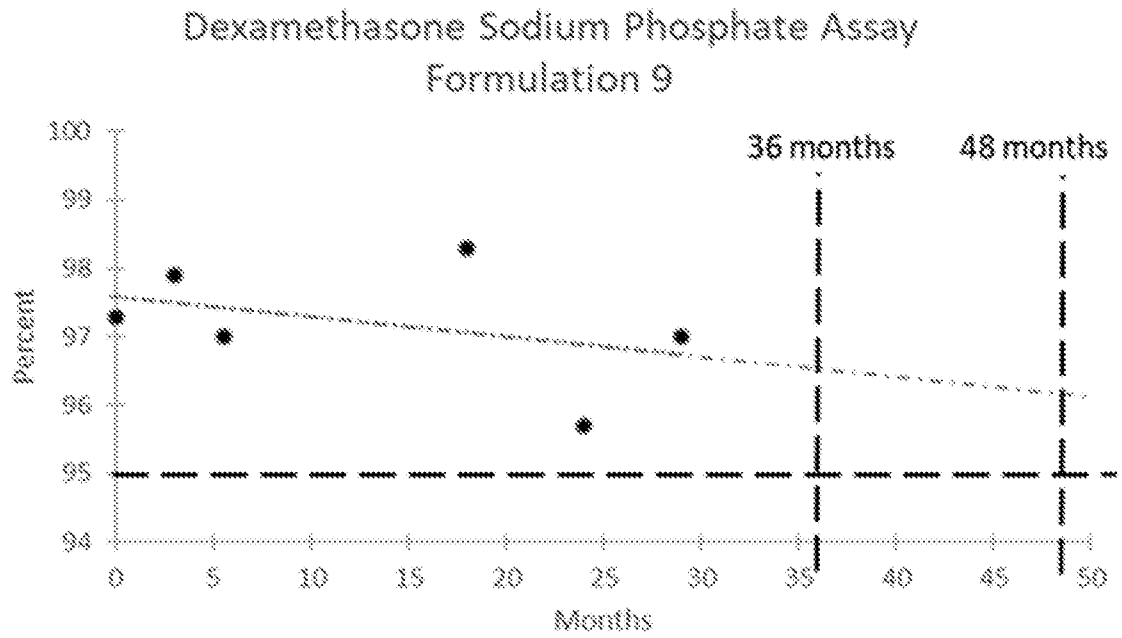


Figure 7

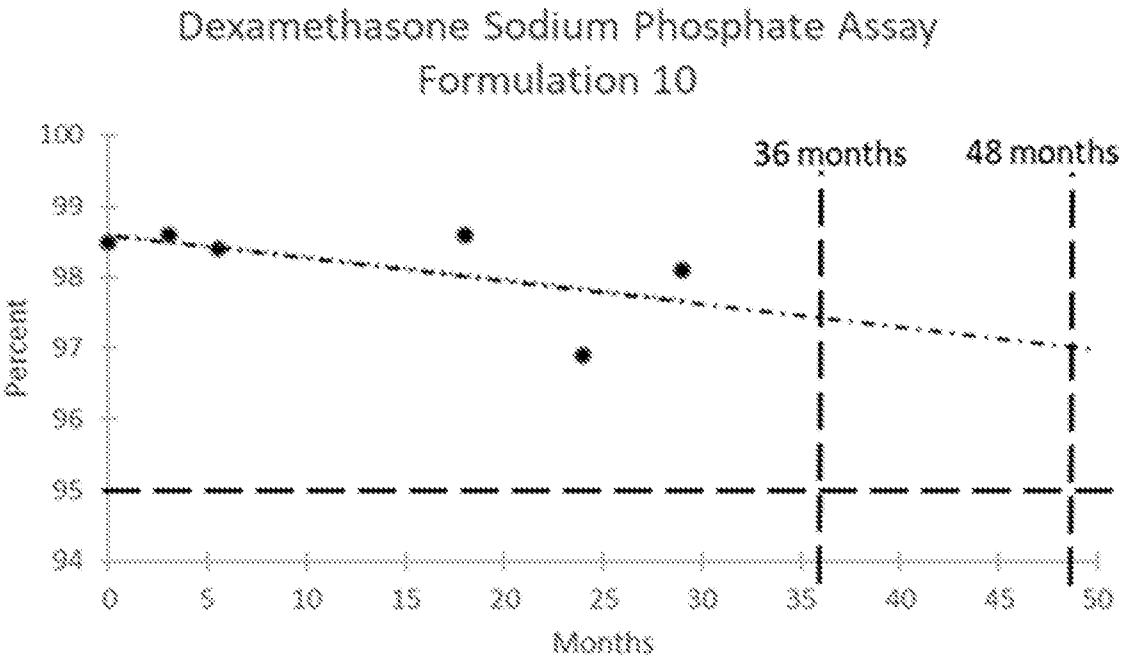


Figure 8

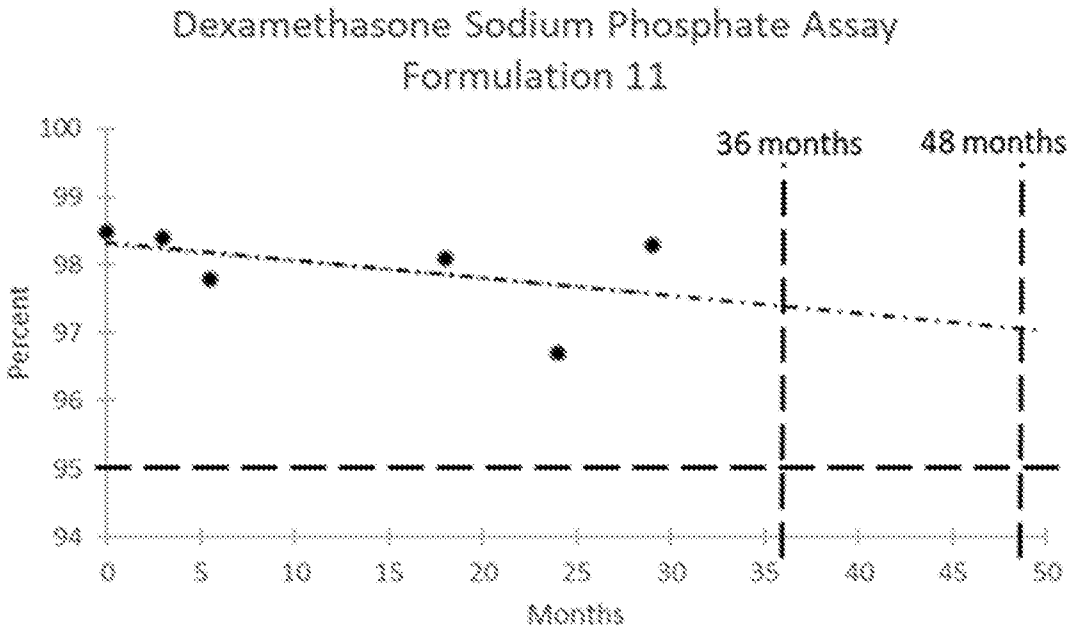


Figure 9

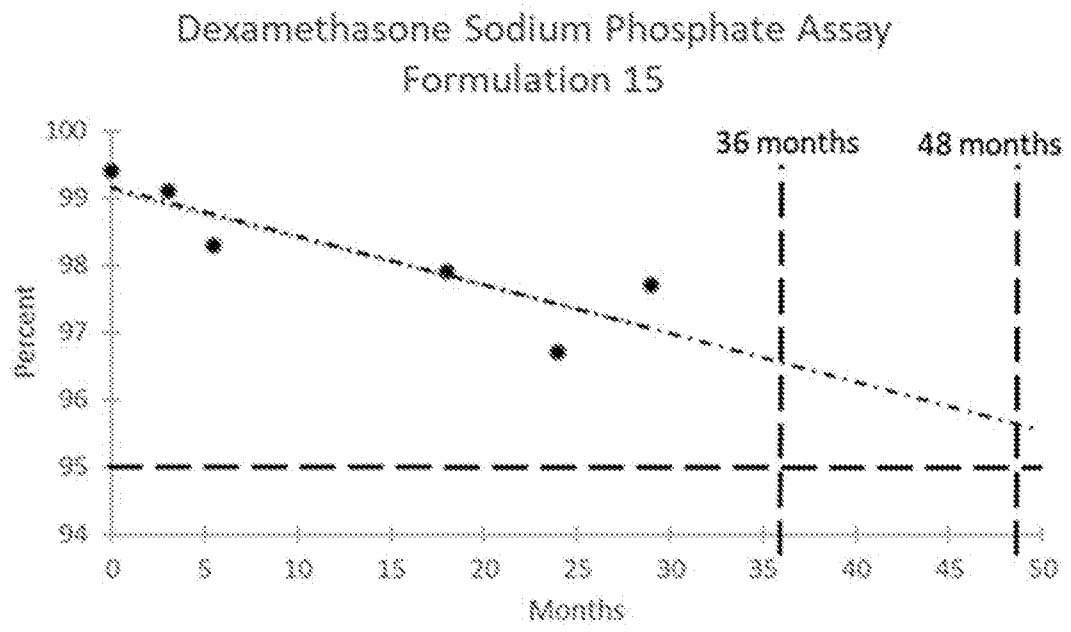


Figure 10

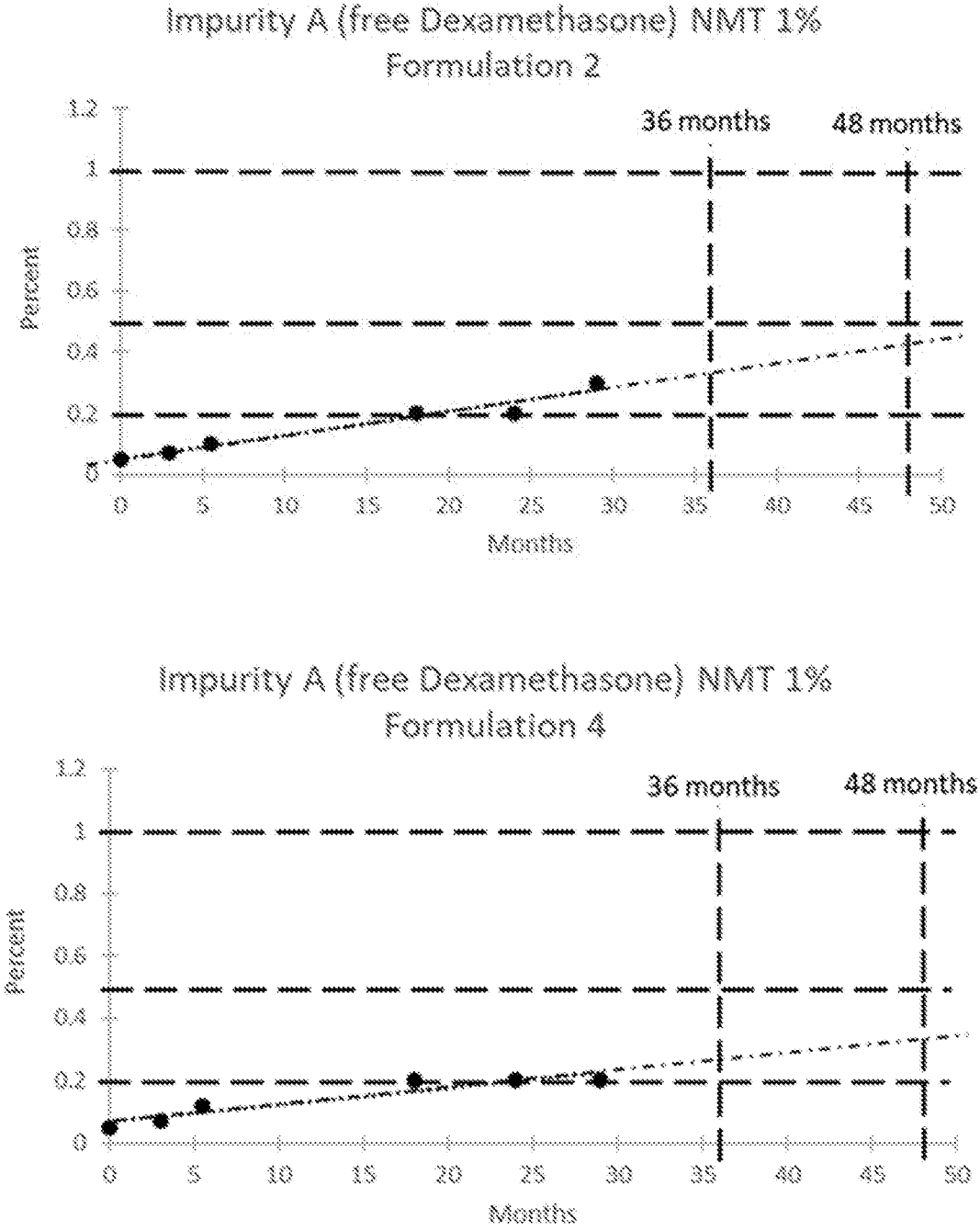

Impurity A (free Dexamethasone) NMT 1%
Formulation 2
36 months
48 months
Percent
1.2
1
0.8
0.6
0.4
0.2
0
0
5
10
15
20
25
30
35
40
45
50
Months
Impurity A (free Dexamethasone) NMT 1%
Formulation 4
36 months
48 months
Percent
1.2
1
0.8
0.6
0.4
0.2
0
0
5
10
15
20
25
30
35
40
45
50
Months

Figure 11

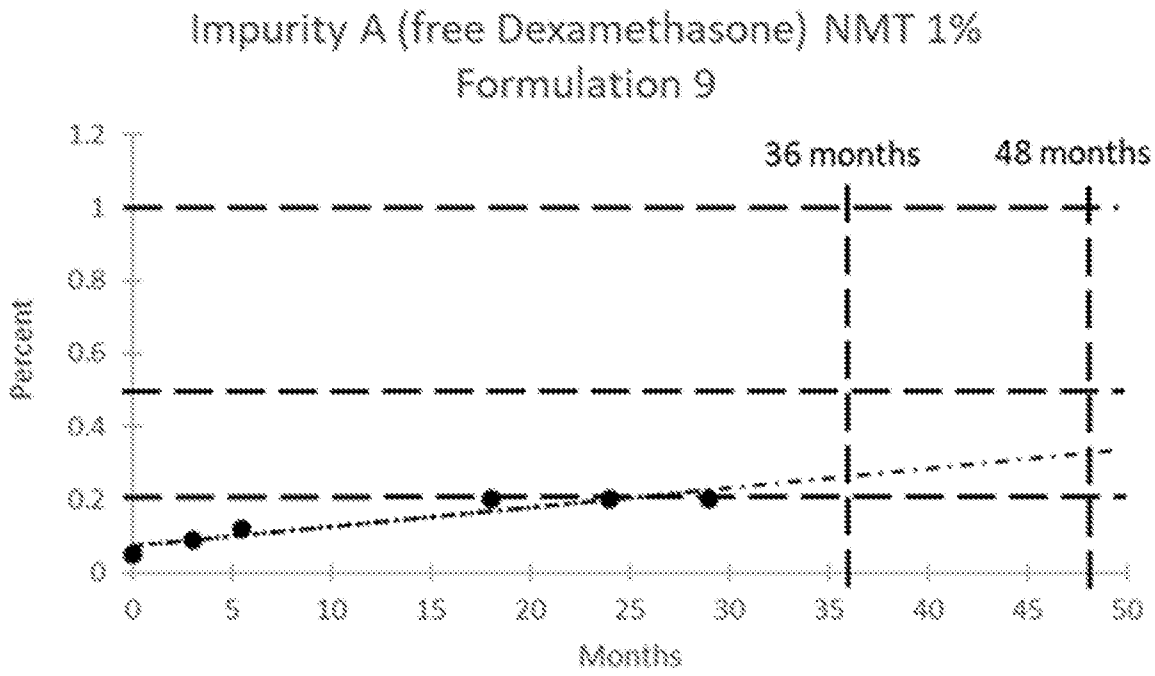


Figure 12

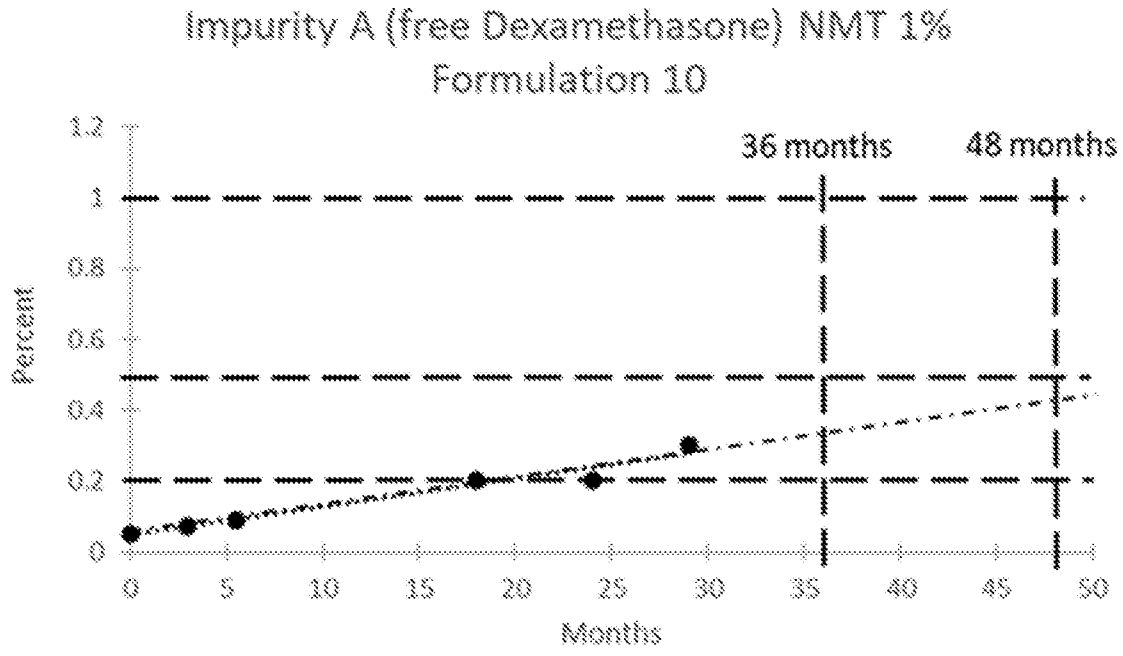


Figure 13

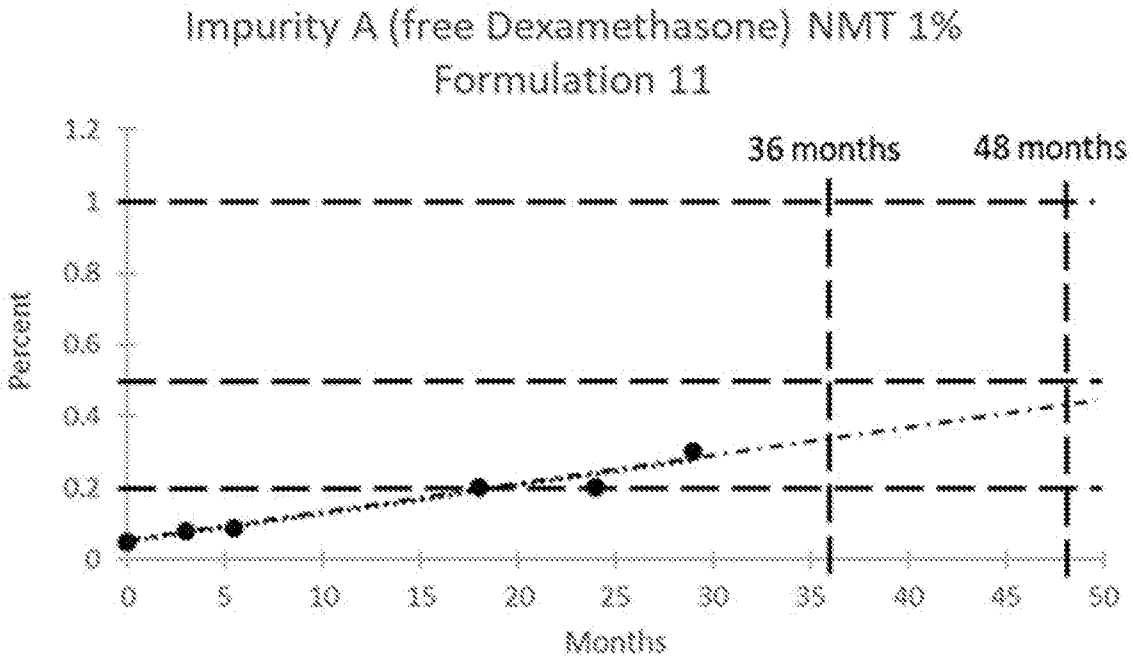


Figure 14

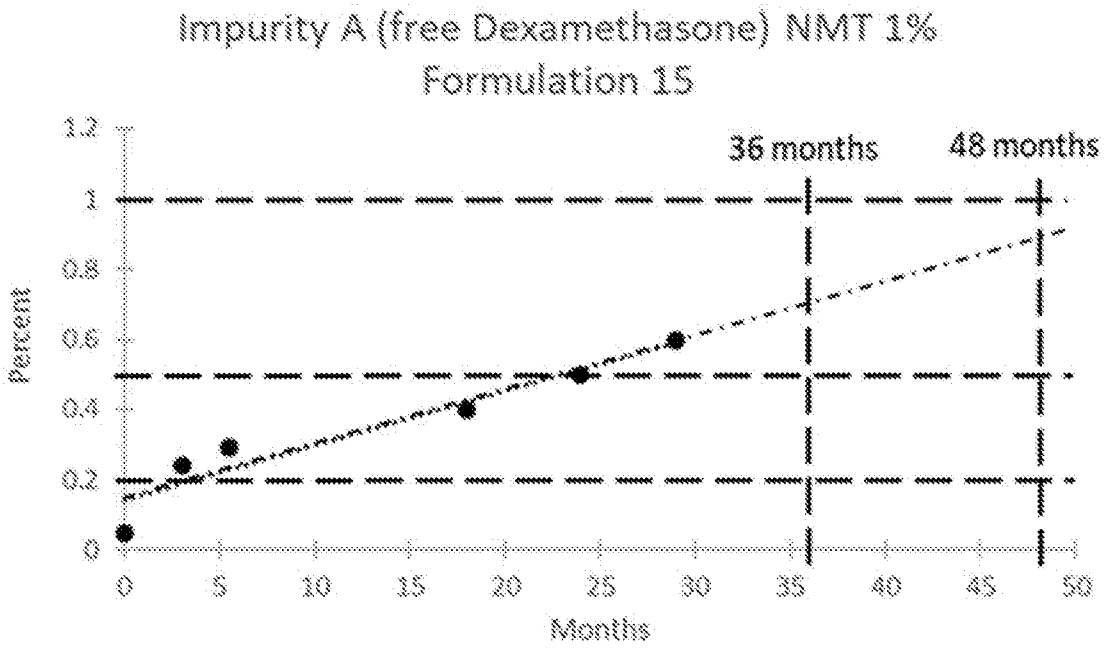


Figure 15

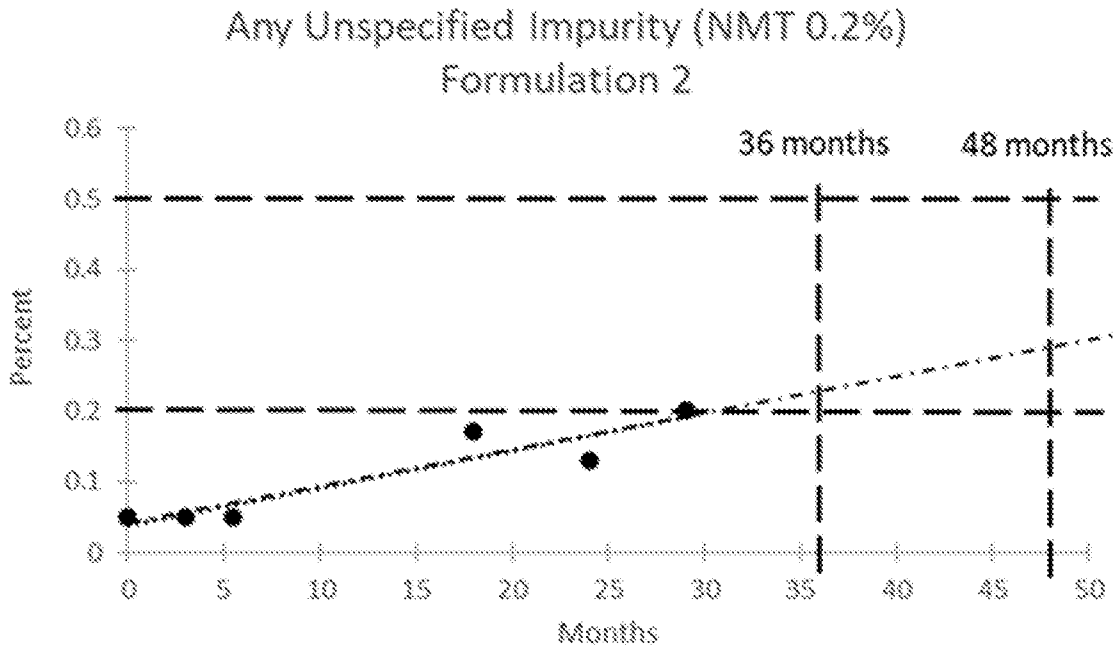


Figure 16

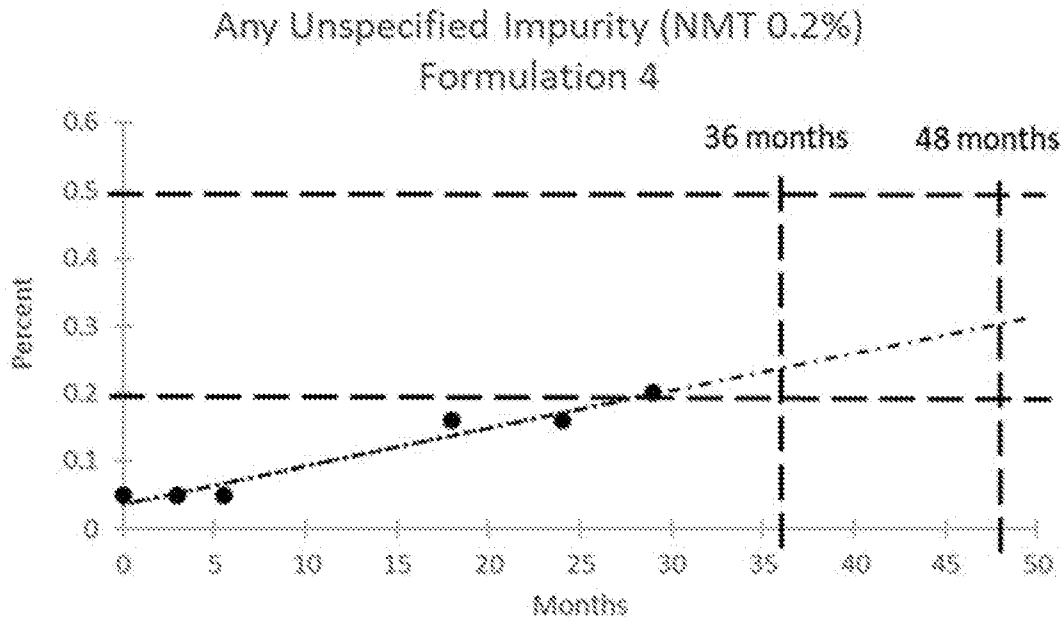


Figure 17

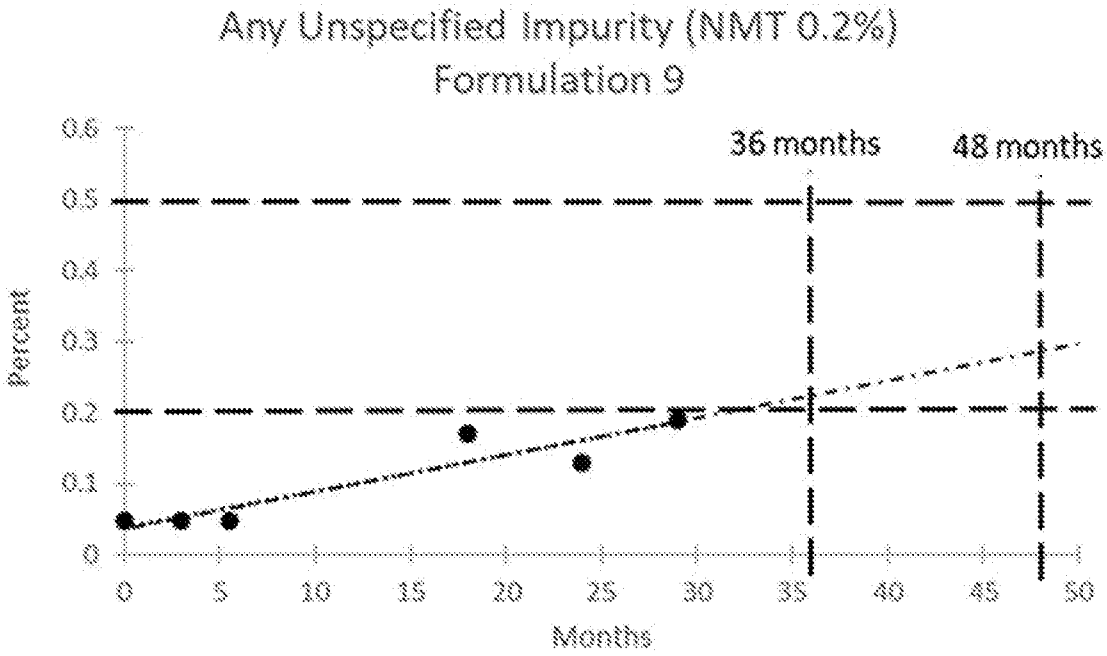


Figure 18

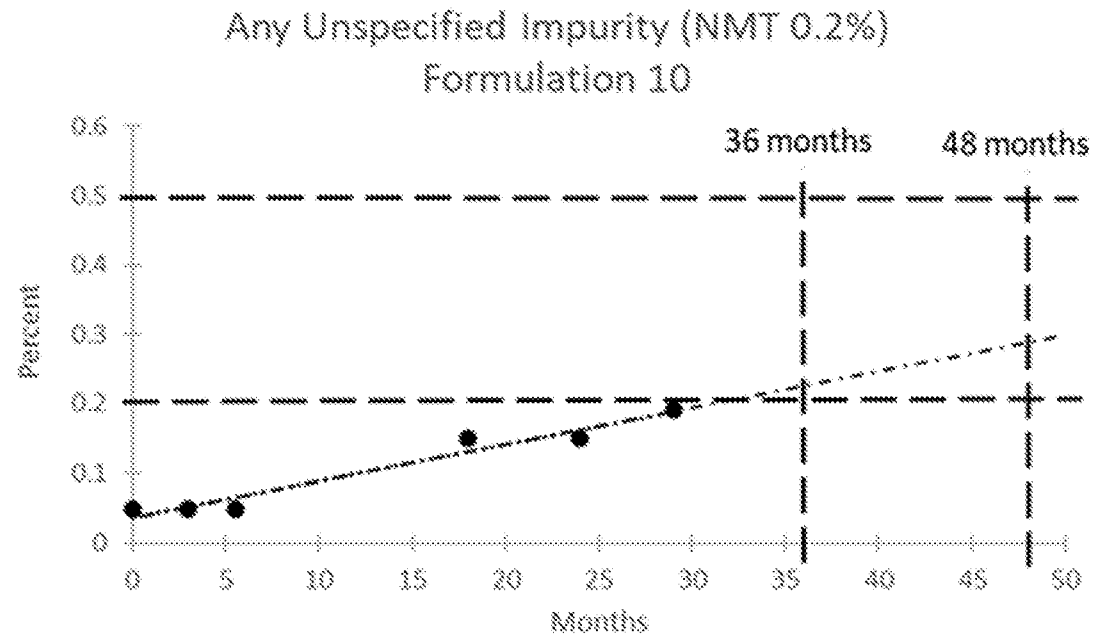


Figure 19

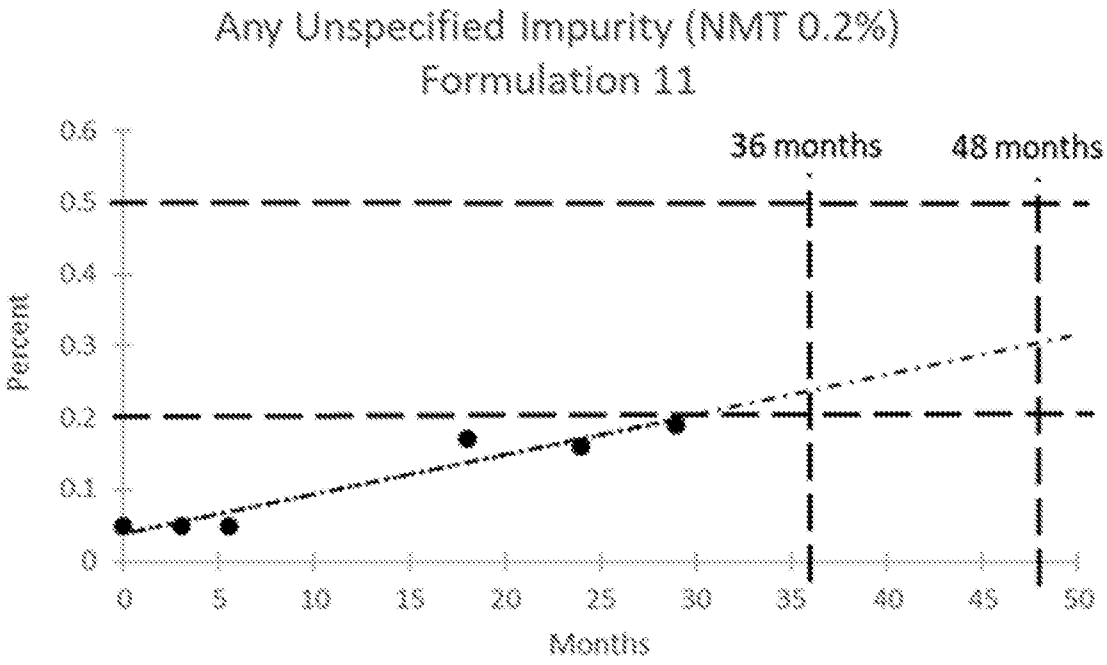


Figure 20

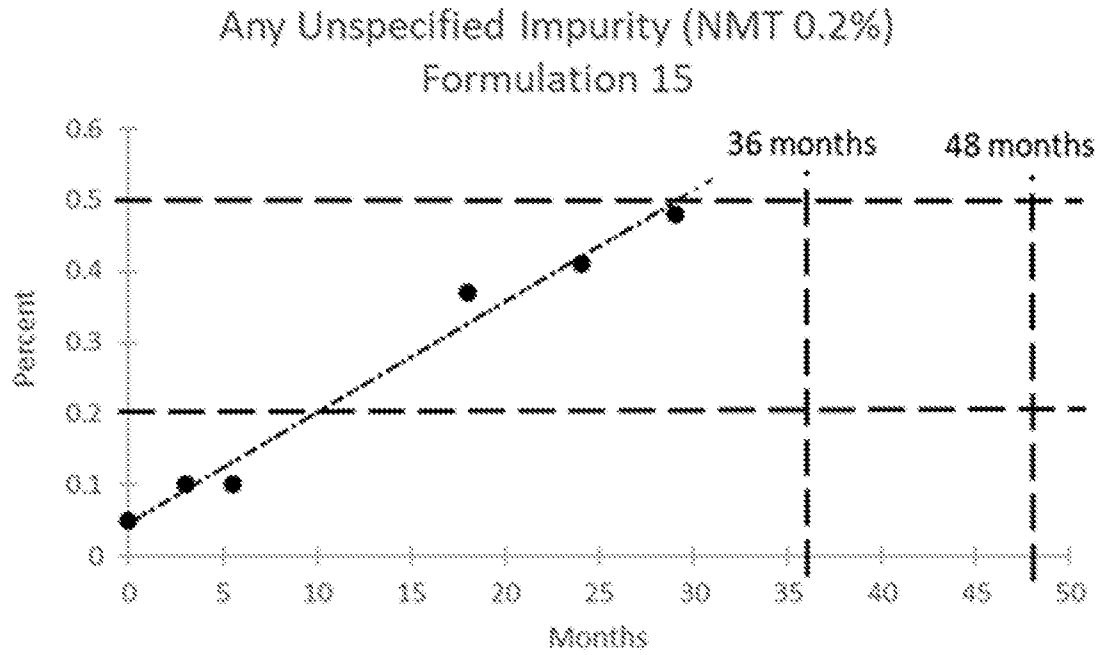


Figure 21

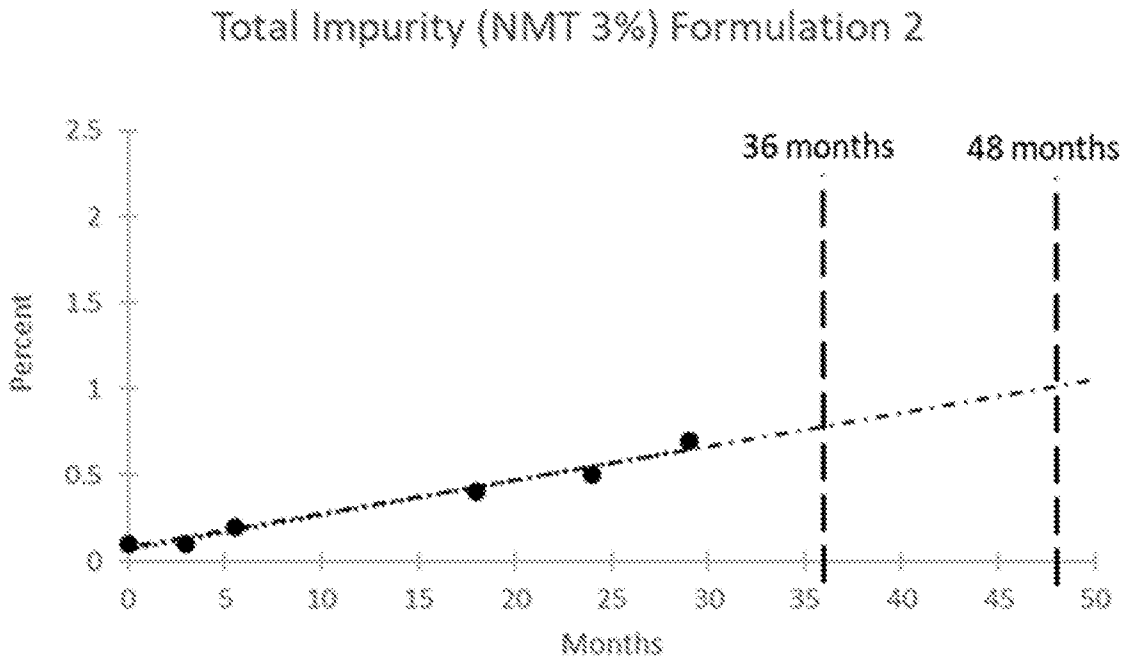


Figure 22

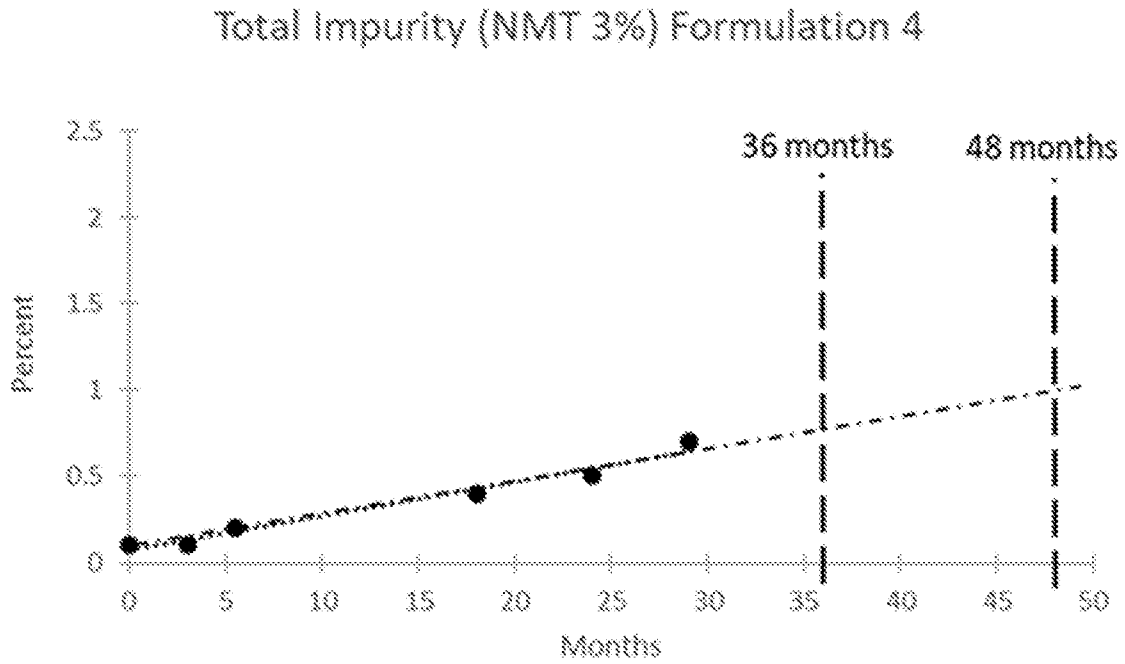


Figure 23

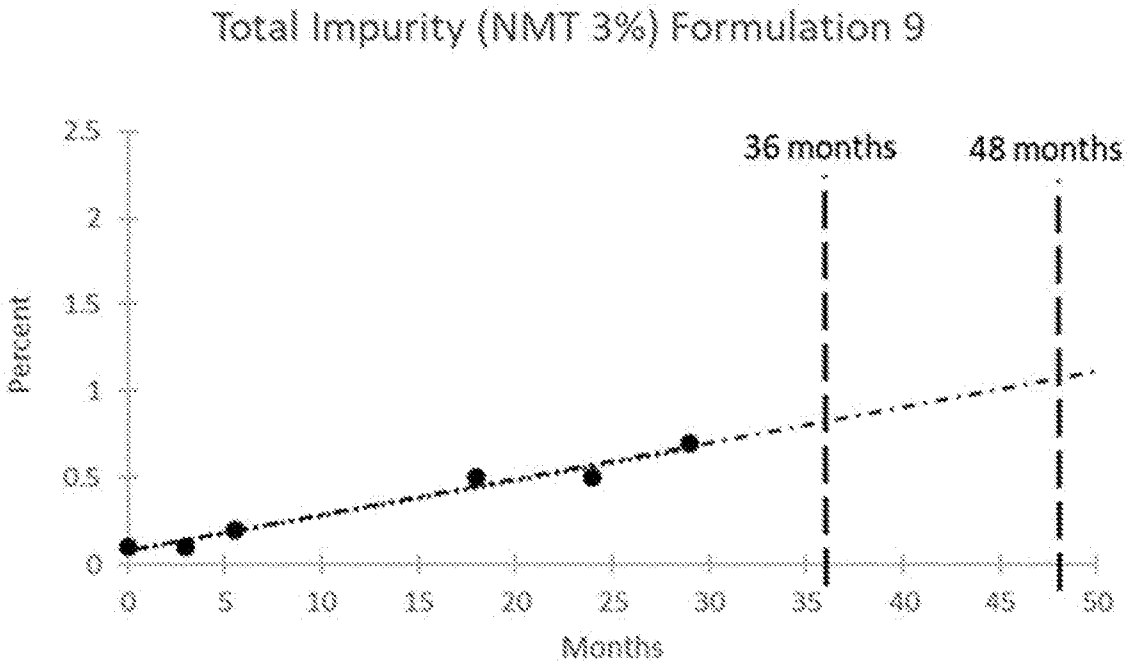


Figure 24

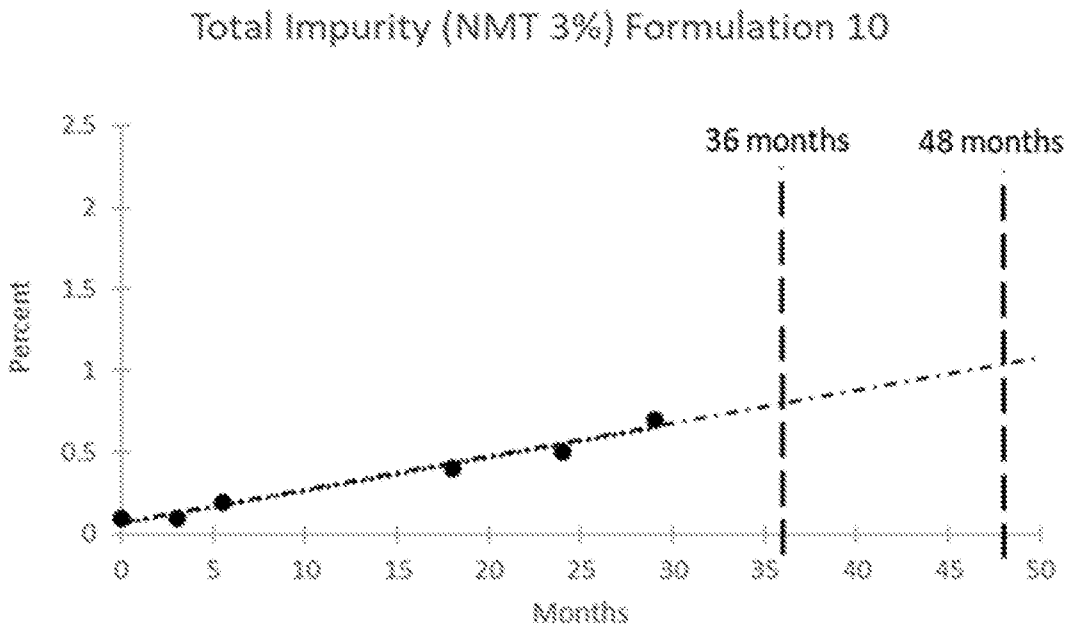


Figure 25

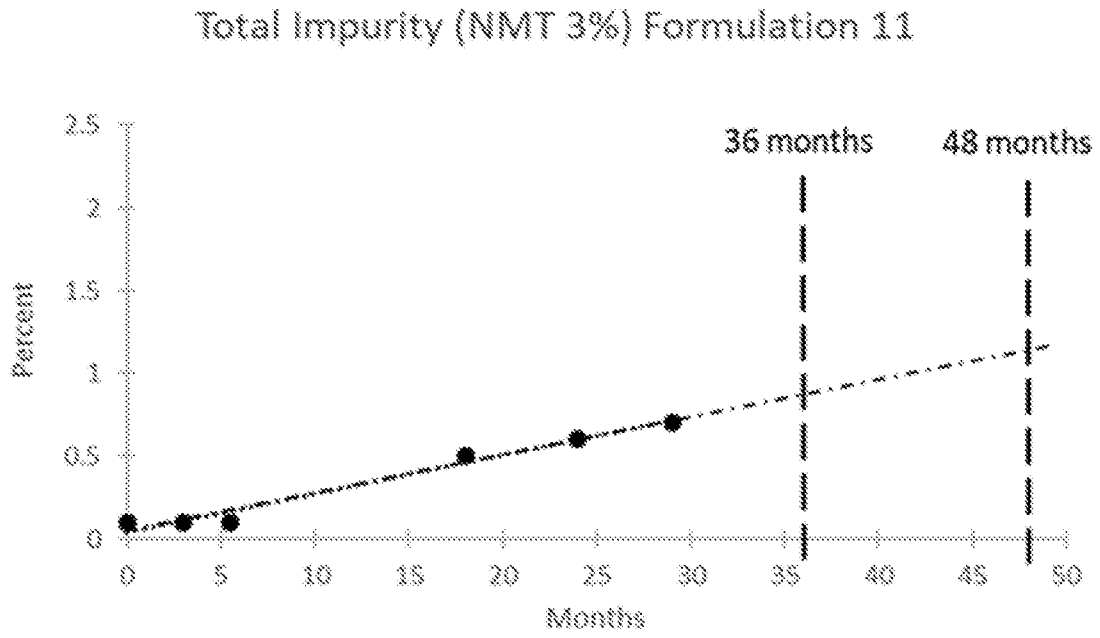


Figure 26

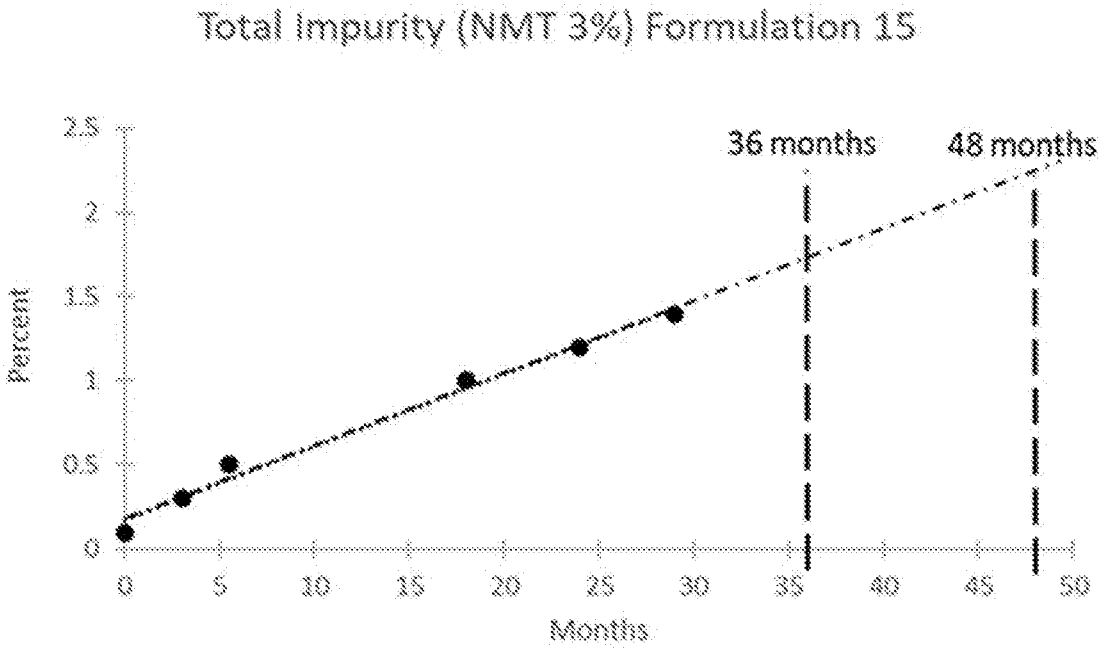
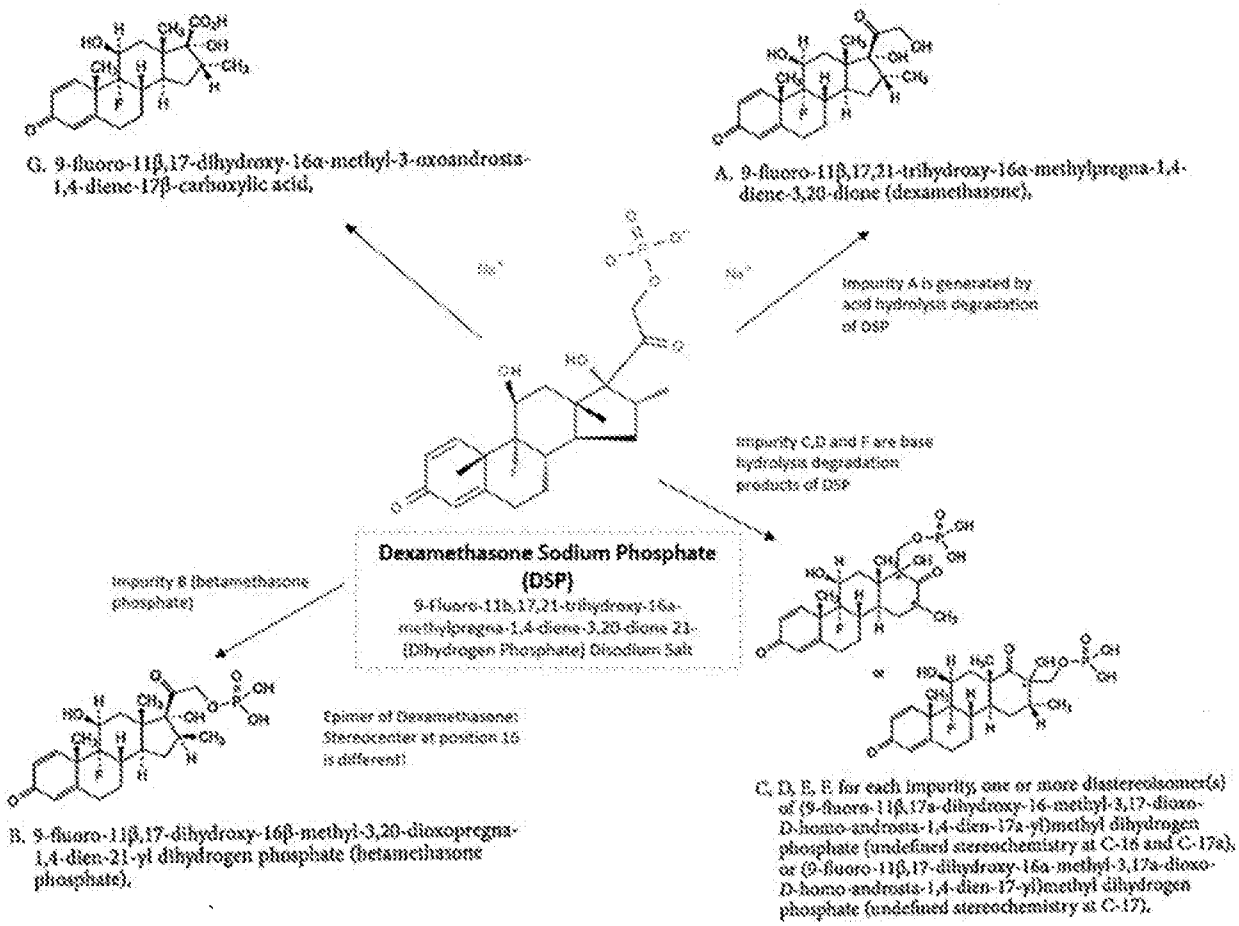
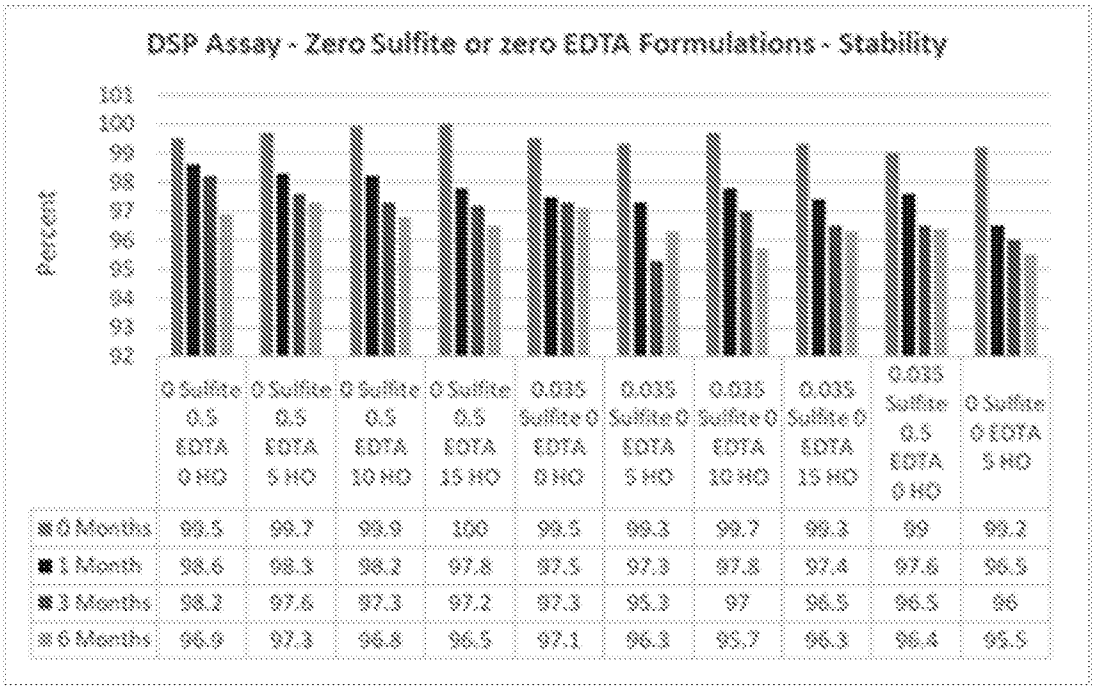


Figure 27



	Equivalent USP Impurity
Impurity A	Dexamethasone
Impurity B	Betamethasone sodium phosphate
Impurity C	USP Impurity a
Impurity D	USP Impurity b
Impurity E	USP Impurity c
Impurity F	USP Impurity d
Impurity G	USP Impurity f

Figure 28


DSP Assay - Zero Sulfite or zero EDTA Formulations - Stability
Percent
101
100
99
98
97
96
95
94
93
92
0 Sulfite 0.5 EDTA 0 HO
0 Sulfite 0.5 EDTA 5 HO
0 Sulfite 0.5 EDTA 10 HO
0 Sulfite 0.5 EDTA 15 HO
0.035 Sulfite 0 EDTA 0 HO
0.035 Sulfite 0 EDTA 5 HO
0.035 Sulfite 0 EDTA 10 HO
0.035 Sulfite 0 EDTA 15 HO
0.035 Sulfite 0.5 EDTA 0 HO
0 Sulfite 0 EDTA 5 HO
0 Months 99.5 99.7 99.9 100 99.5 99.3 99.7 99.3 99 99.2
1 Month 98.6 98.3 98.2 97.8 97.5 97.3 97.8 97.4 97.6 96.5
3 Months 98.2 97.6 97.3 97.2 97.3 95.3 97 96.5 96.5 96
6 Months 96.9 97.3 96.8 96.5 97.1 96.3 96.7 96.3 96.4 95.5

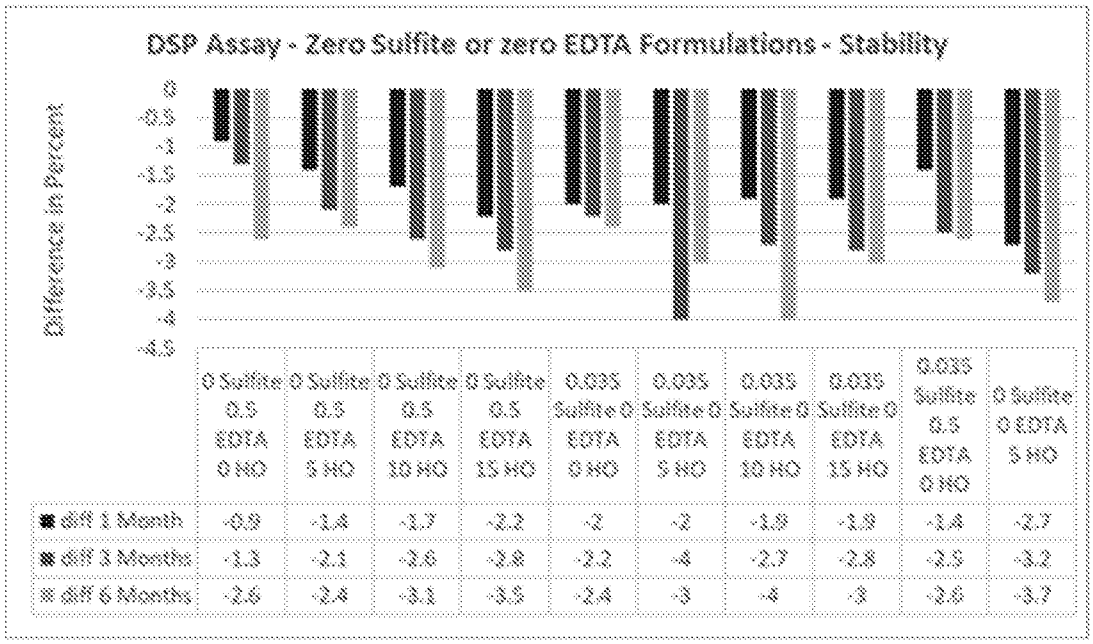

DSP Assay - Zero Sulfite or zero EDTA Formulations - Stability
Difference in Percent
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
-4.5
0 Sulfite 0.5 EDTA 0 HO
0 Sulfite 0.5 EDTA 5 HO
0 Sulfite 0.5 EDTA 10 HO
0 Sulfite 0.5 EDTA 15 HO
0.035 Sulfite 0 EDTA 0 HO
0.035 Sulfite 0 EDTA 5 HO
0.035 Sulfite 0 EDTA 10 HO
0.035 Sulfite 0 EDTA 15 HO
0.035 Sulfite 0.5 EDTA 0 HO
0 Sulfite 0 EDTA 5 HO
diff 1 Month -0.9 -1.4 -1.7 -2.2 -2 -2 -1.9 -1.9 -1.4 -2.7
diff 3 Months -1.3 -2.1 -3.6 -2.8 -2.2 -4 -2.7 -2.8 -2.5 -3.2
diff 6 Months -2.6 -2.4 -3.1 -3.5 -2.4 -3 -4 -3 -2.6 -3.7

Figure 29

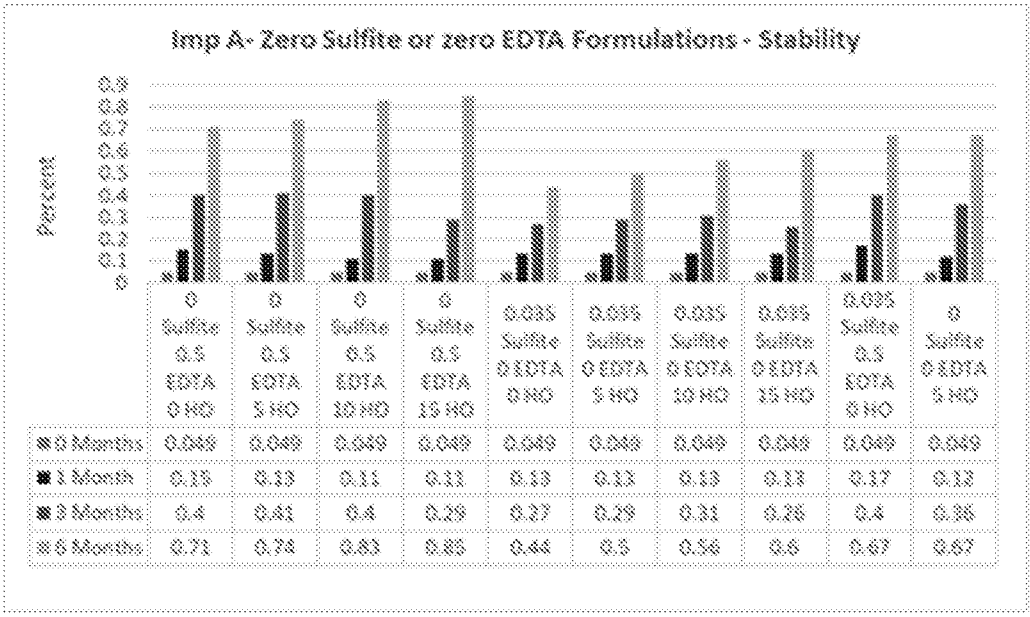


Figure 30

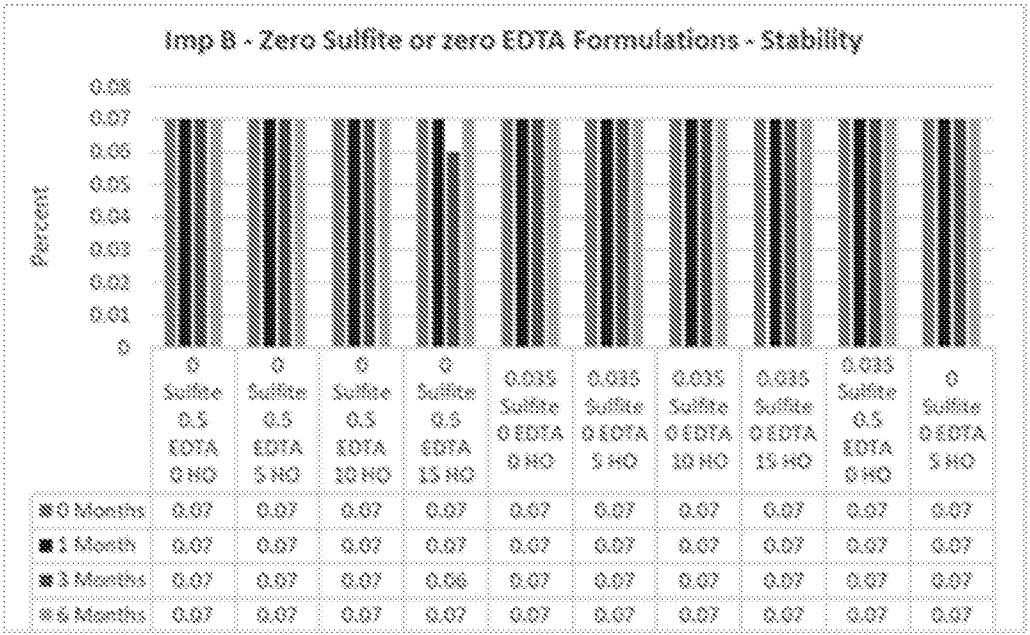


Figure 31

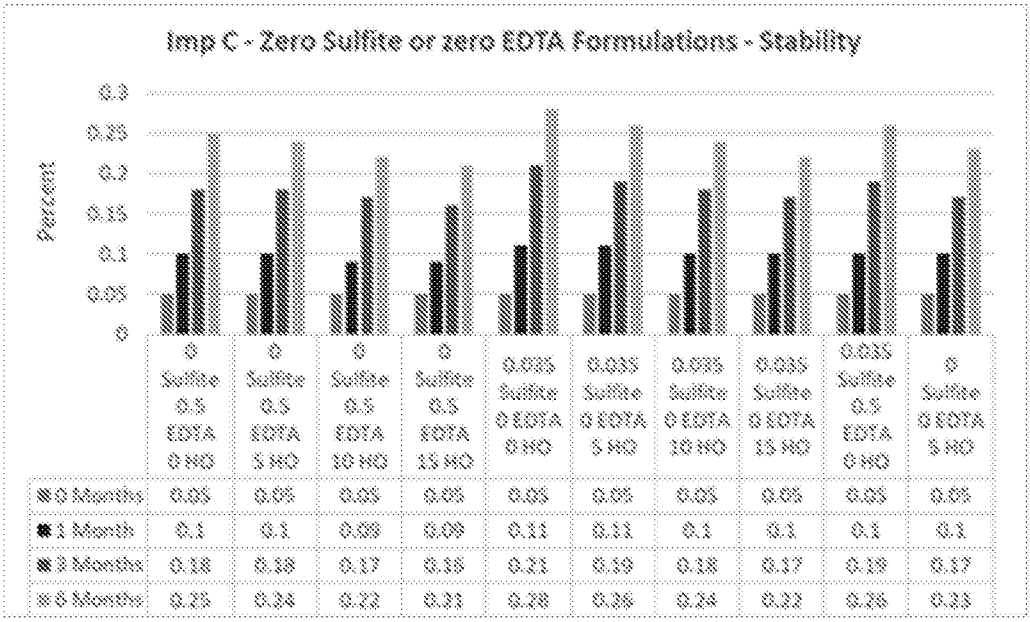


Figure 32

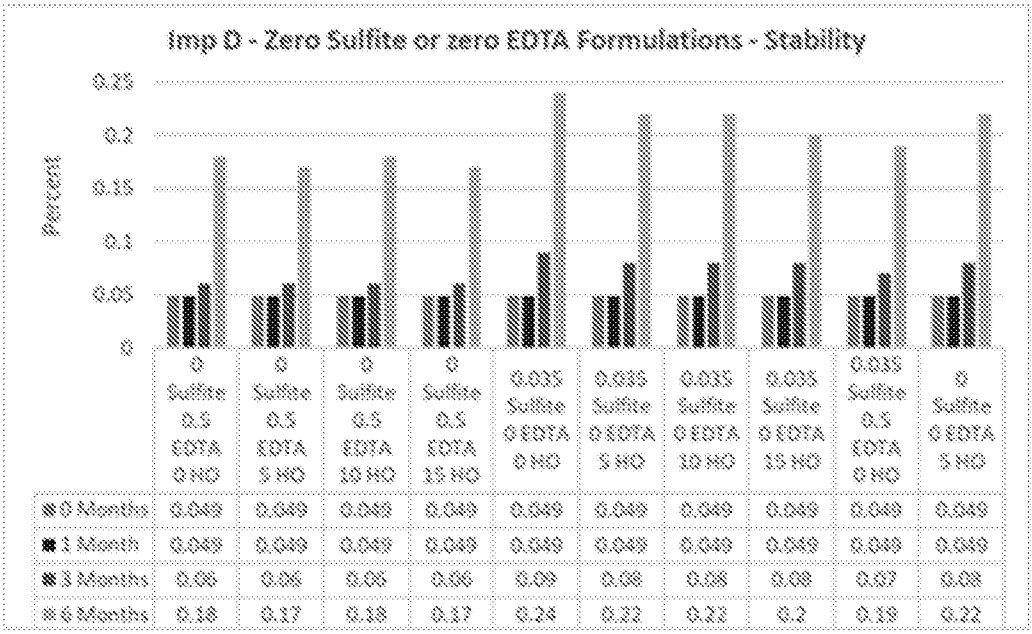


Figure 33

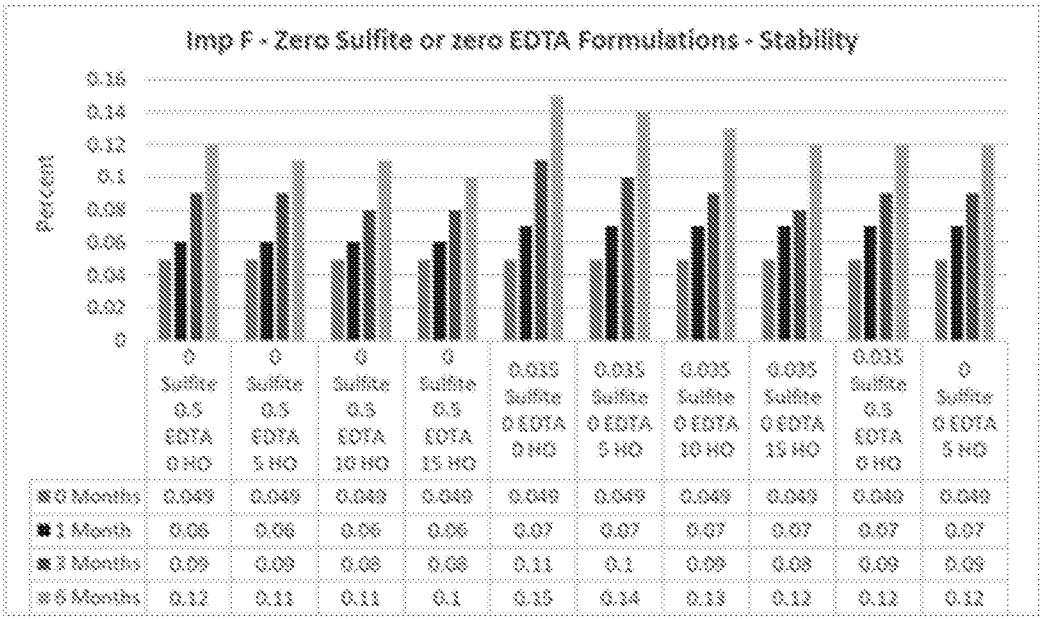


Figure 34

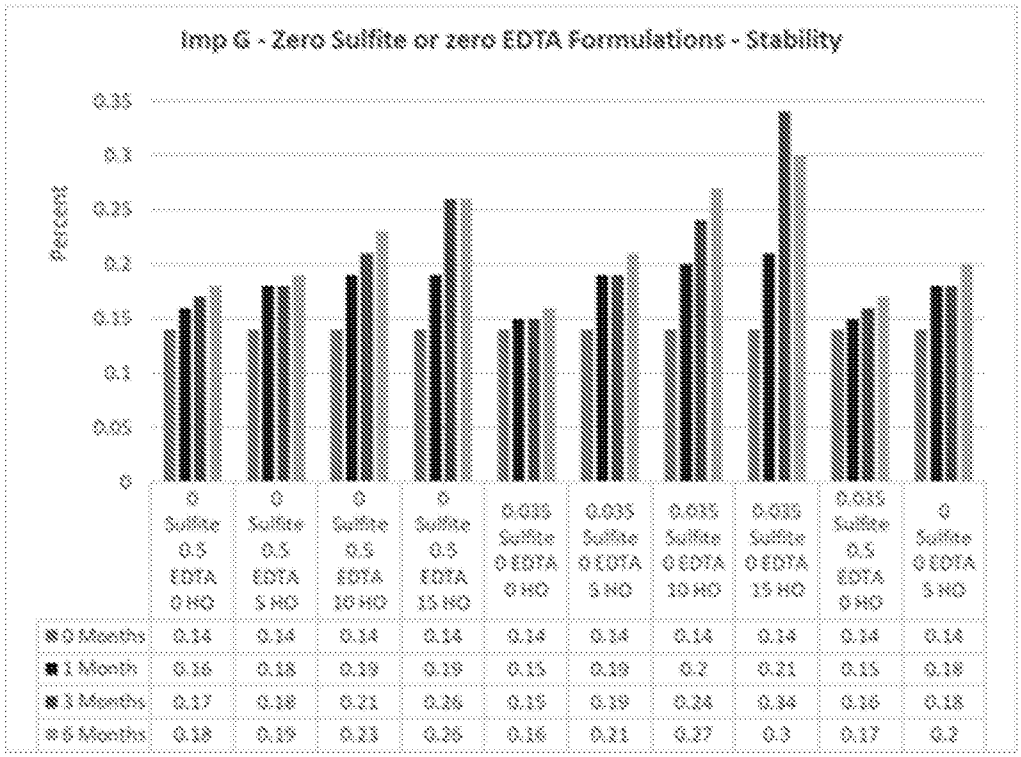


Figure 35

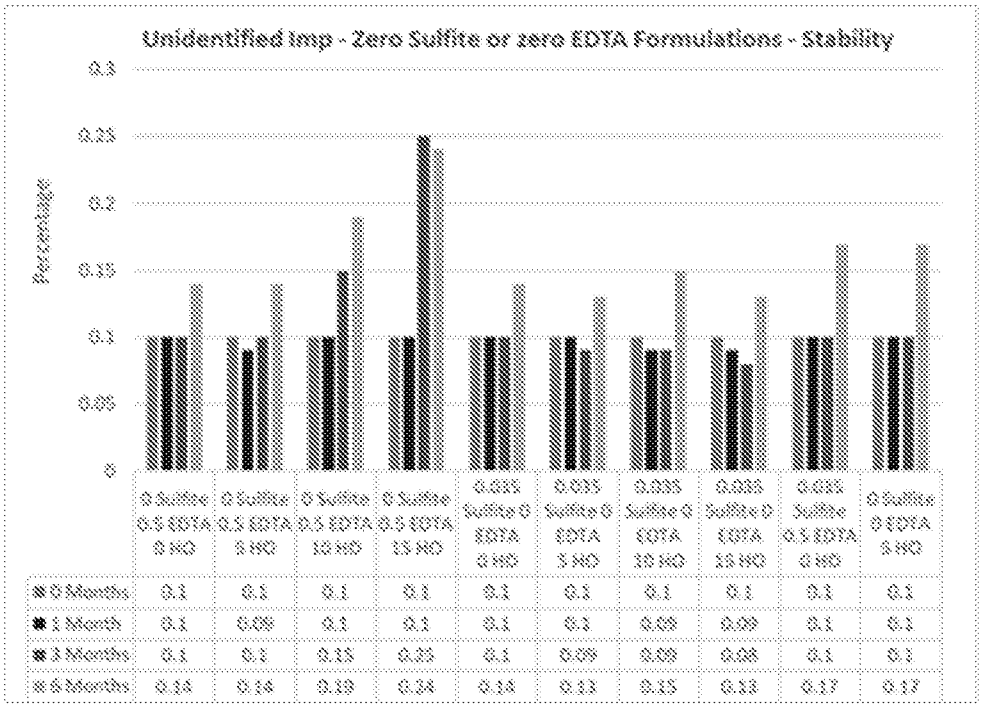


Figure 36

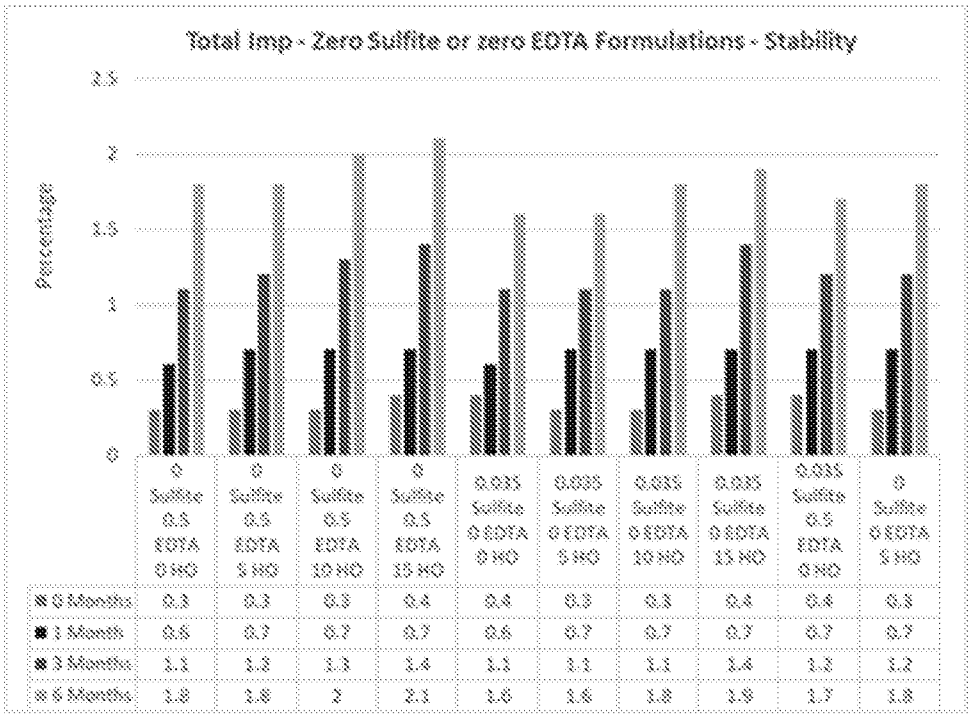


Figure 37

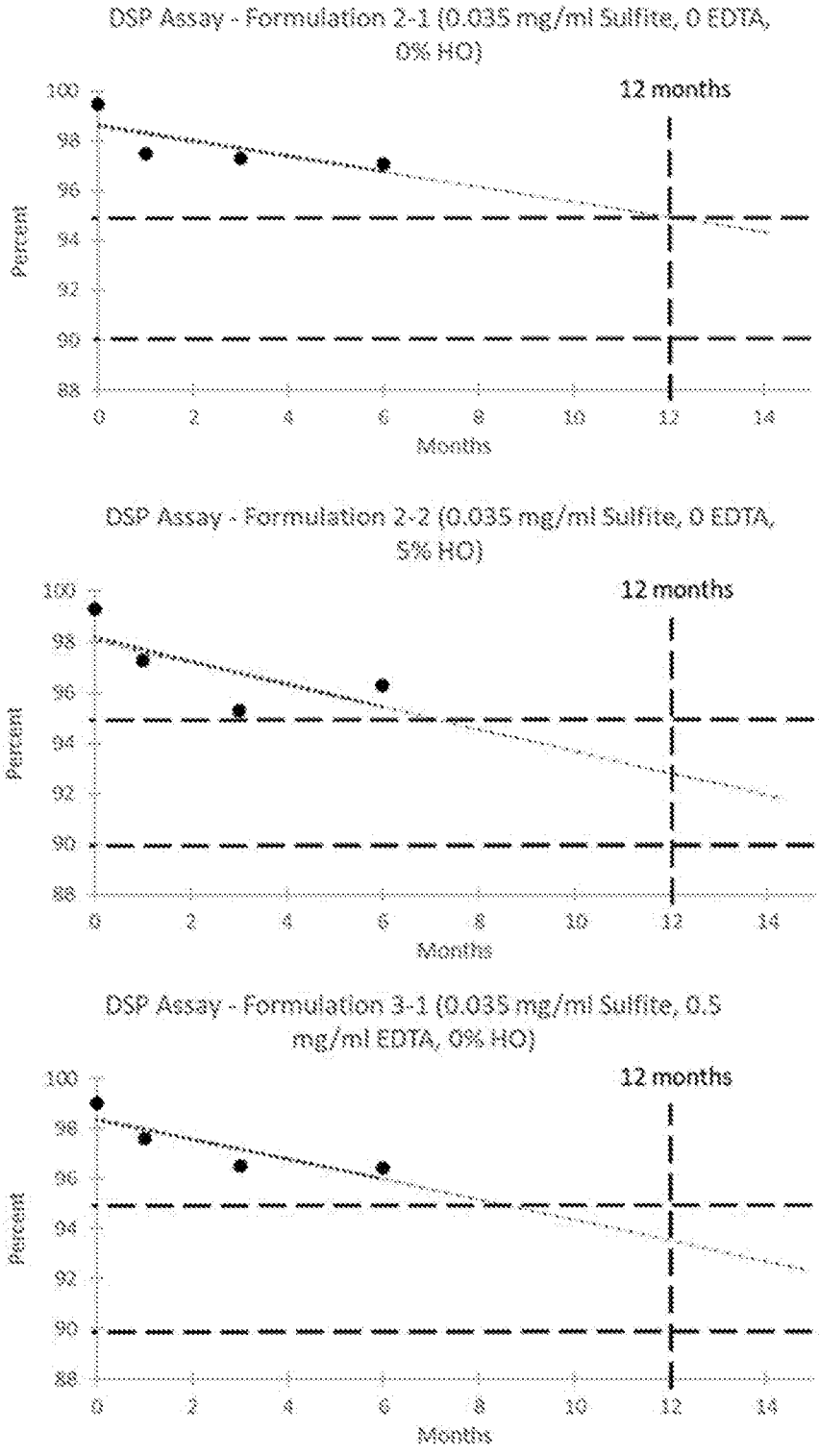

DSP Assay - Formulation 2-1 (0.035 mg/ml Sulfite, 0 EDTA, 0% HO)
12 months
Percent
100
98
96
94
92
90
88
0
2
4
6
8
10
12
14
Months
DSP Assay - Formulation 2-2 (0.035 mg/ml Sulfite, 0 EDTA, 5% HO)
12 months
Percent
Months
DSP Assay - Formulation 3-1 (0.035 mg/ml Sulfite, 0.5 mg/ml EDTA, 0% HO)
12 months
Percent
Months

Figure 38

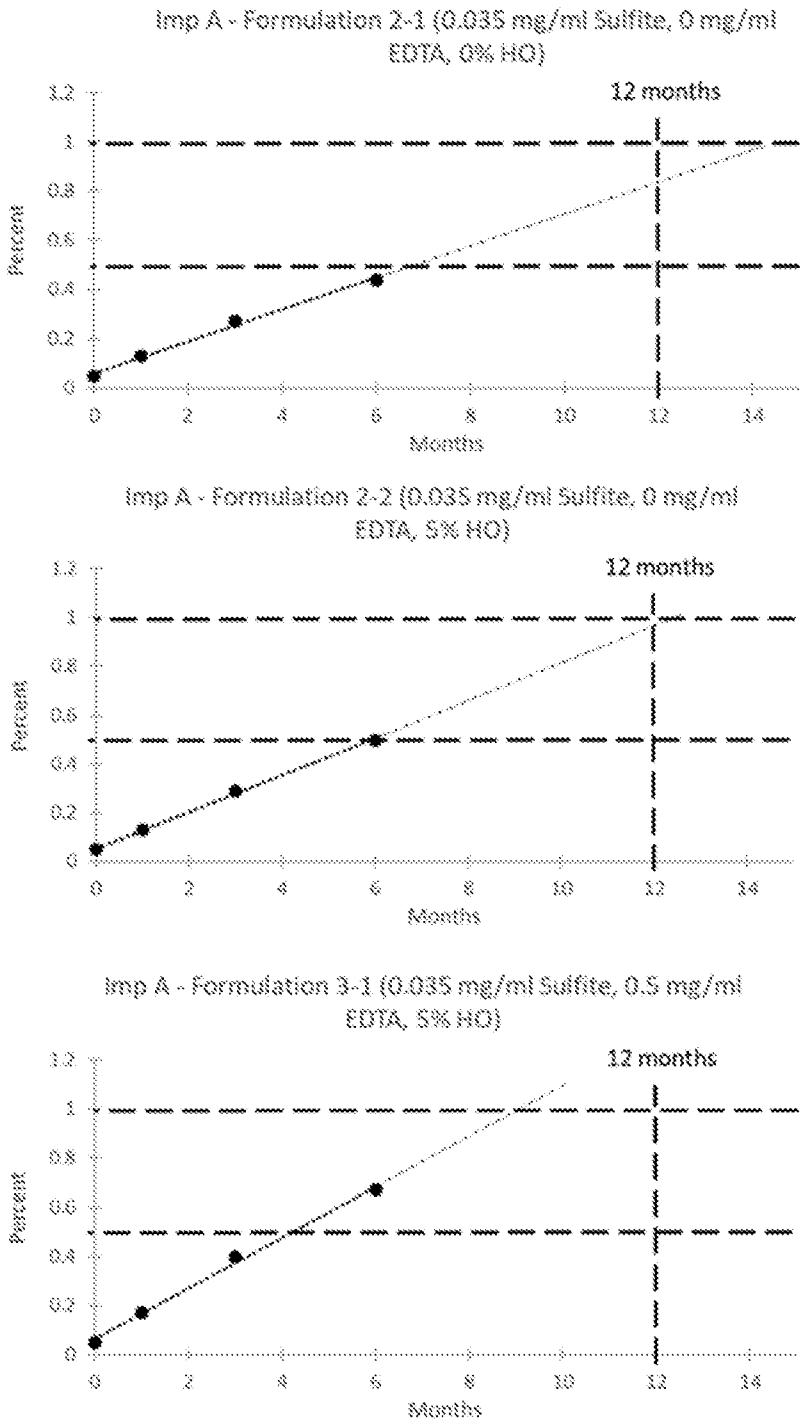

Imp A - Formulation 2-1 (0.035 mg/ml Sulfite, 0 mg/ml EDTA, 0% HO)
12 months
Percent
Months
Imp A - Formulation 2-2 (0.035 mg/ml Sulfite, 0 mg/ml EDTA, 5% HO)
12 months
Percent
Months
Imp A - Formulation 3-1 (0.035 mg/ml Sulfite, 0.5 mg/ml EDTA, 5% HO)
12 months
Percent
Months

Figure 39

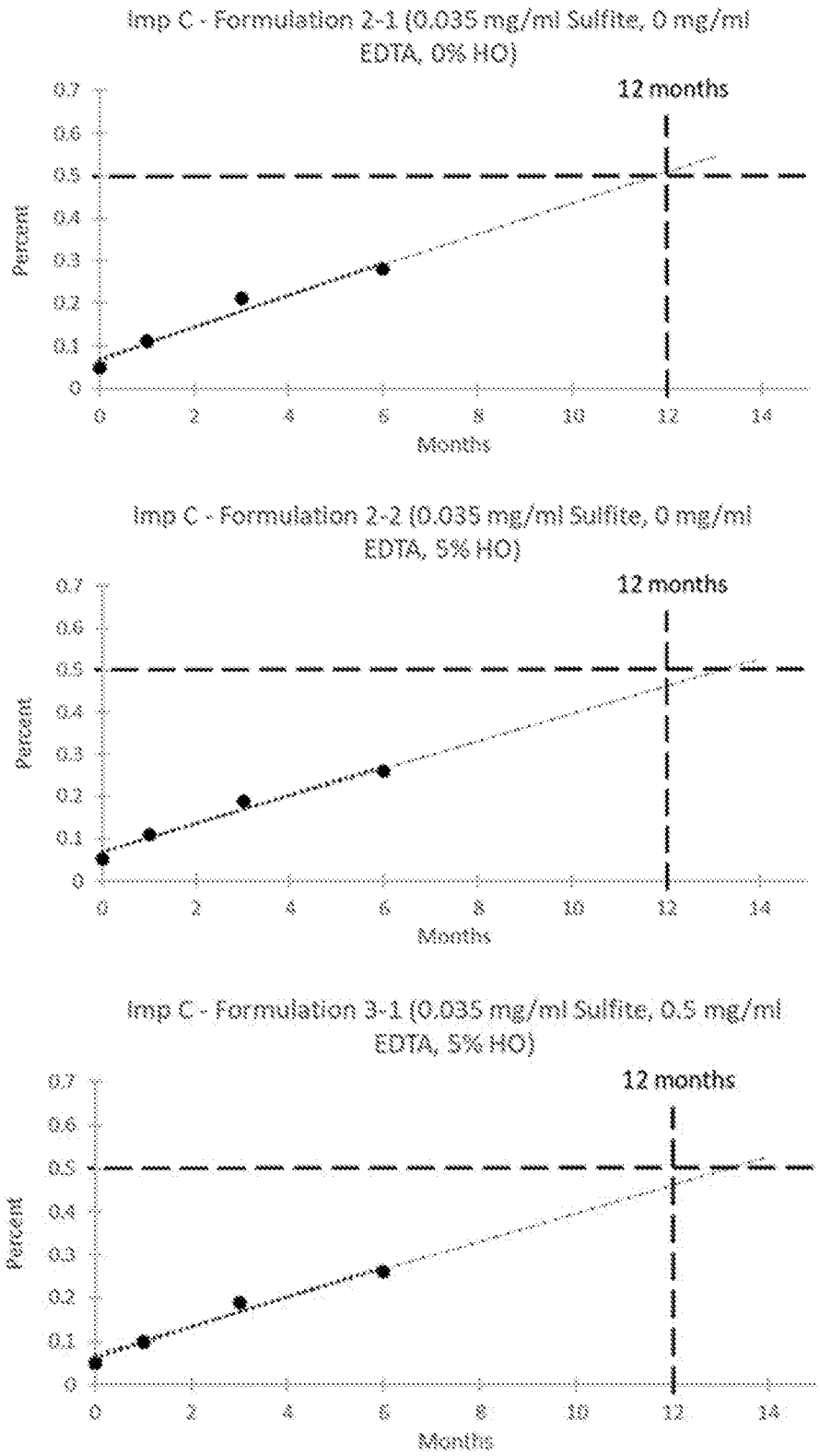

Imp C - Formulation 2-1 (0.035 mg/ml Sulfite, 0 mg/ml EDTA, 0% HO)
12 months
Percent
Months
Imp C - Formulation 2-2 (0.035 mg/ml Sulfite, 0 mg/ml EDTA, 5% HO)
12 months
Percent
Months
Imp C - Formulation 3-1 (0.035 mg/ml Sulfite, 0.5 mg/ml EDTA, 5% HO)
12 months
Percent
Months

Figure 40

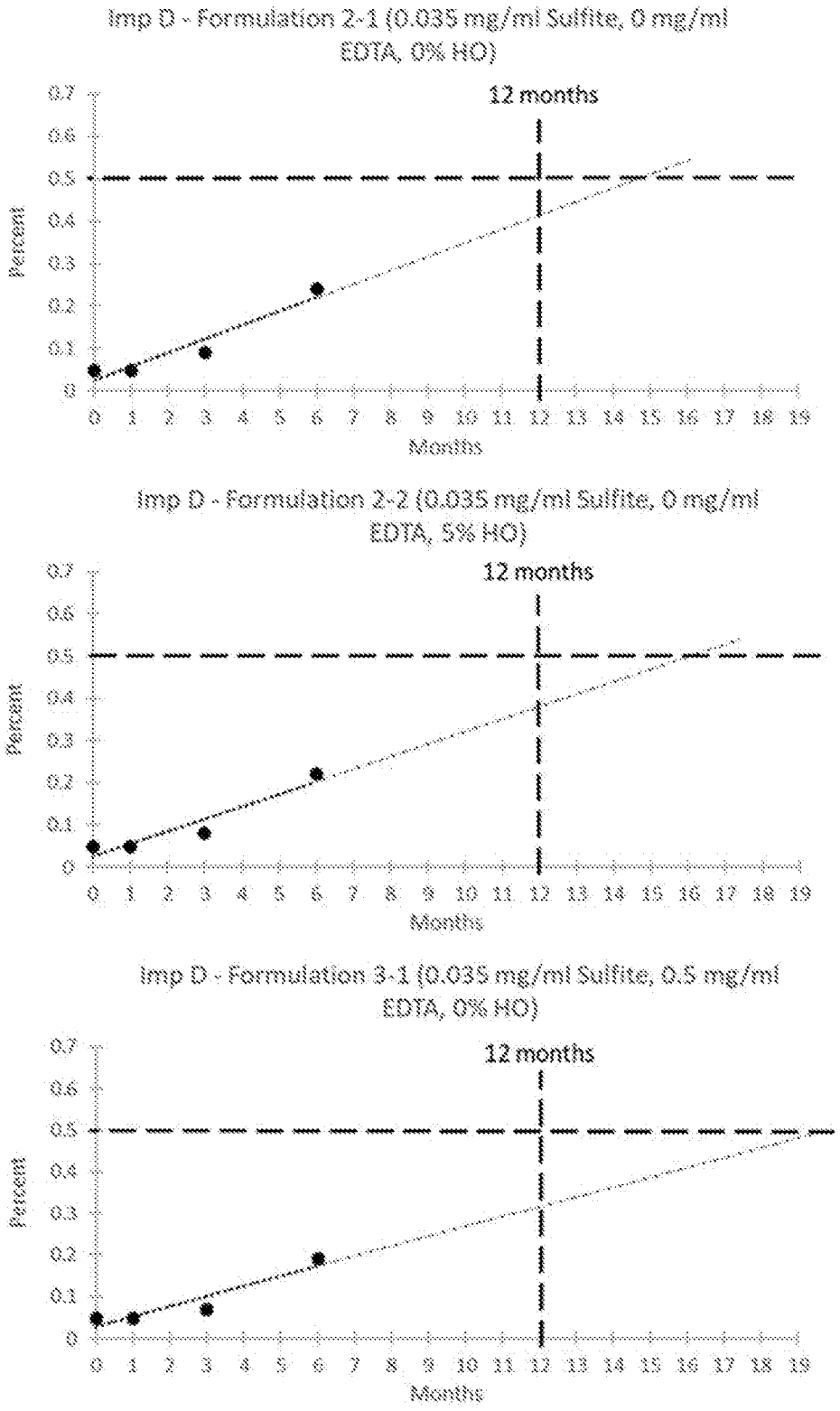

Imp D - Formulation 2-1 (0.035 mg/ml Sulfite, 0 mg/ml EDTA, 0% HO)
12 months
Percent
Months
Imp D - Formulation 2-2 (0.035 mg/ml Sulfite, 0 mg/ml EDTA, 5% HO)
12 months
Percent
Months
Imp D - Formulation 3-1 (0.035 mg/ml Sulfite, 0.5 mg/ml EDTA, 0% HO)
12 months
Percent
Months

Figure 41

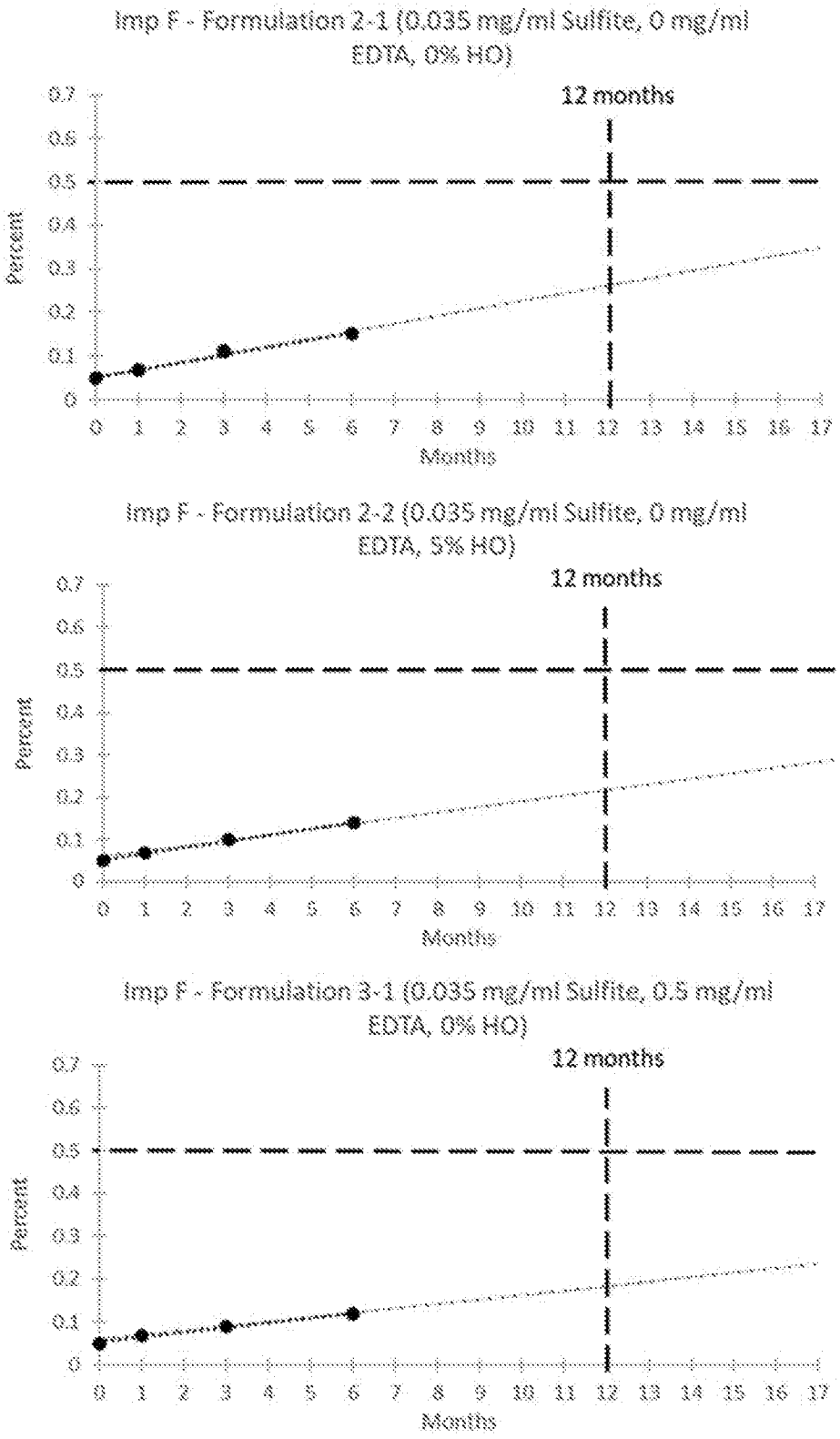

Imp F - Formulation 2-1 (0.035 mg/ml Sulfite, 0 mg/ml EDTA, 0% HO)
12 months
Percent
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Months
Imp F - Formulation 2-2 (0.035 mg/ml Sulfite, 0 mg/ml EDTA, 5% HO)
12 months
Percent
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Months
Imp F - Formulation 3-1 (0.035 mg/ml Sulfite, 0.5 mg/ml EDTA, 0% HO)
12 months
Percent
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Months

Figure 42

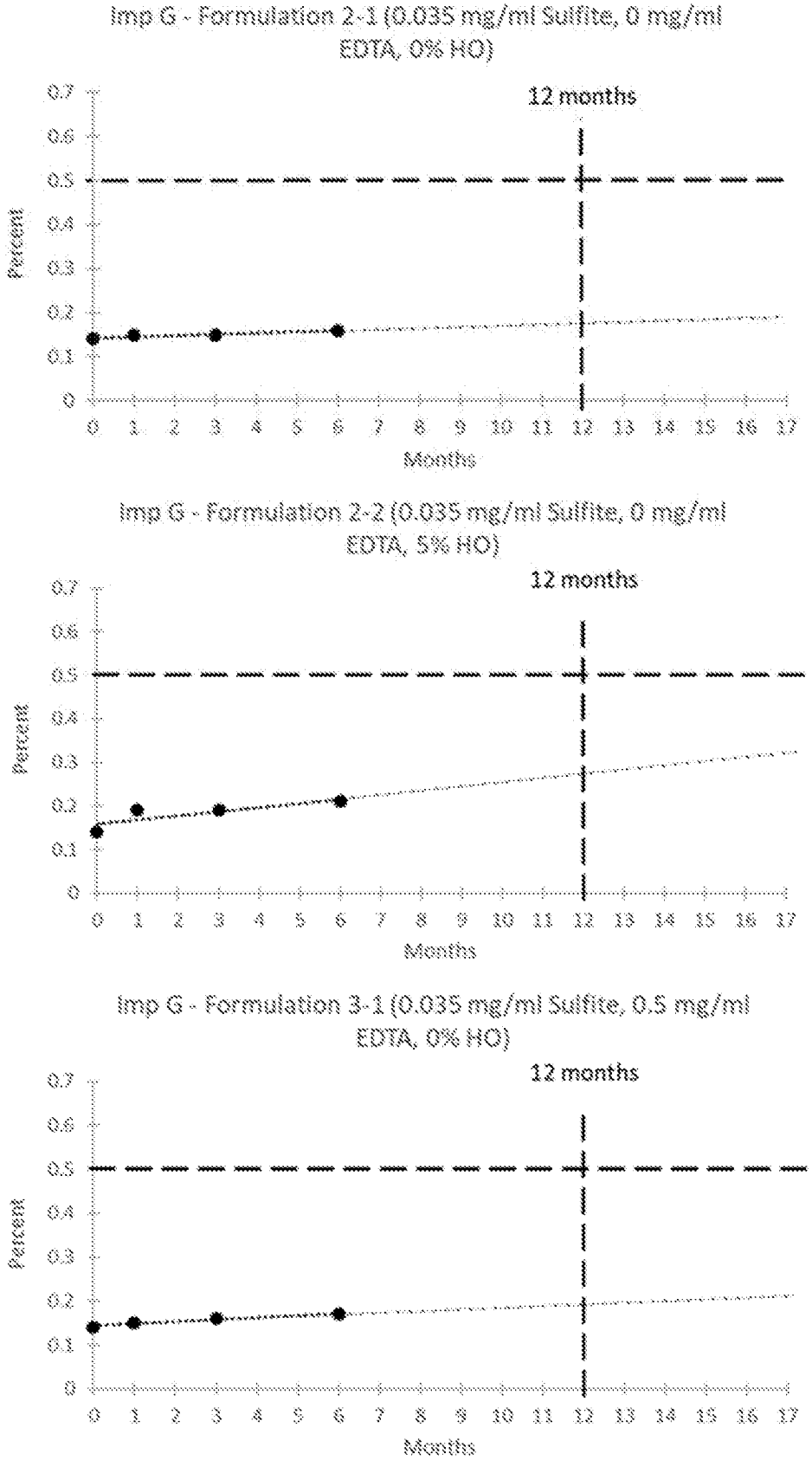

Imp G - Formulation 2-1 (0.035 mg/ml Sulfite, 0 mg/ml EDTA, 0% HO)
12 months
Percent
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Months
Imp G - Formulation 2-2 (0.035 mg/ml Sulfite, 0 mg/ml EDTA, 5% HO)
12 months
Percent
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Months
Imp G - Formulation 3-1 (0.035 mg/ml Sulfite, 0.5 mg/ml EDTA, 0% HO)
12 months
Percent
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Months

Figure 43

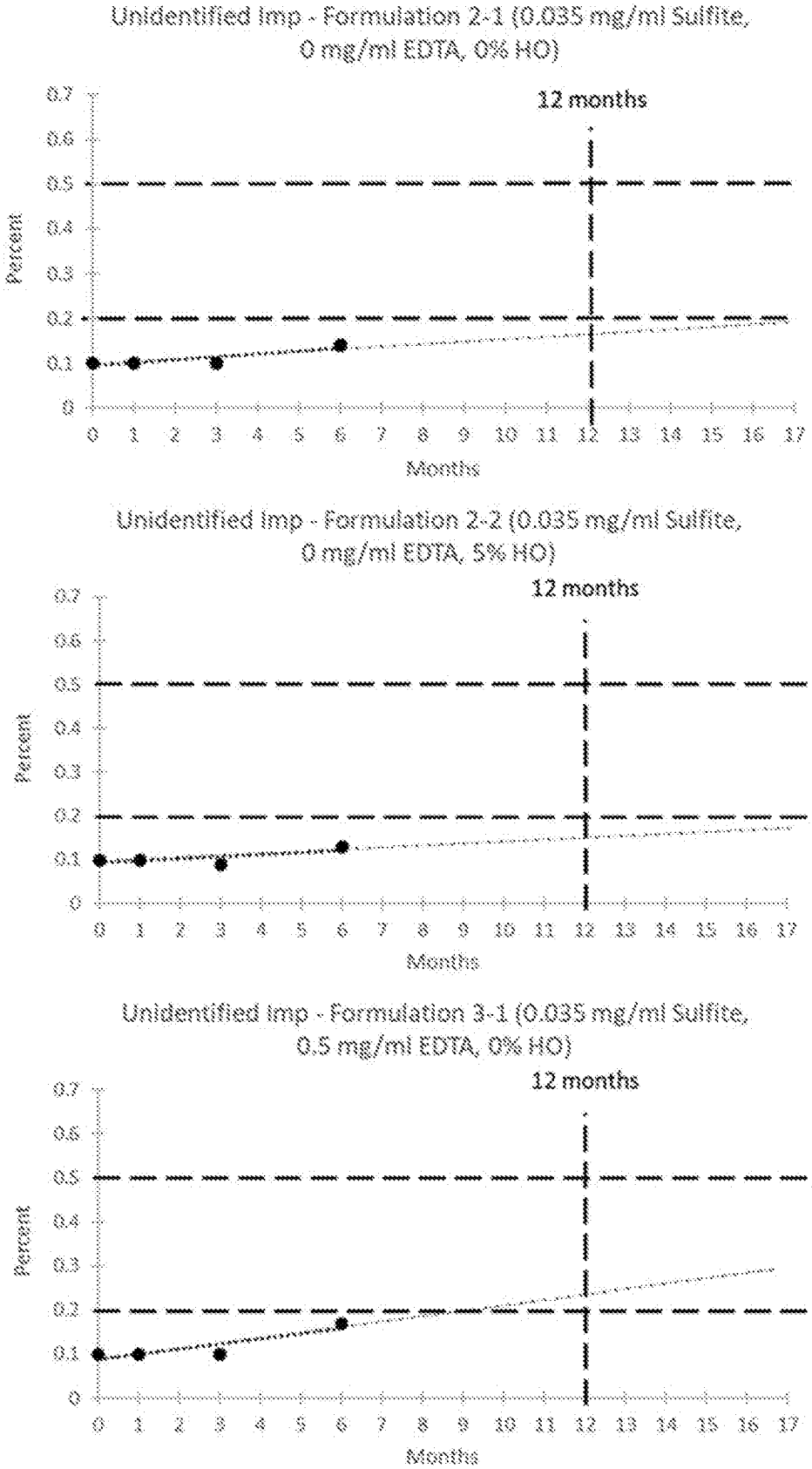

Unidentified Imp - Formulation 2-1 (0.035 mg/ml Sulfite, 0 mg/ml EDTA, 0% HO)
12 months
Percent
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Months
Unidentified Imp - Formulation 2-2 (0.035 mg/ml Sulfite, 0 mg/ml EDTA, 5% HO)
12 months
Percent
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Months
Unidentified Imp - Formulation 3-1 (0.035 mg/ml Sulfite, 0.5 mg/ml EDTA, 0% HO)
12 months
Percent
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Months

Figure 44

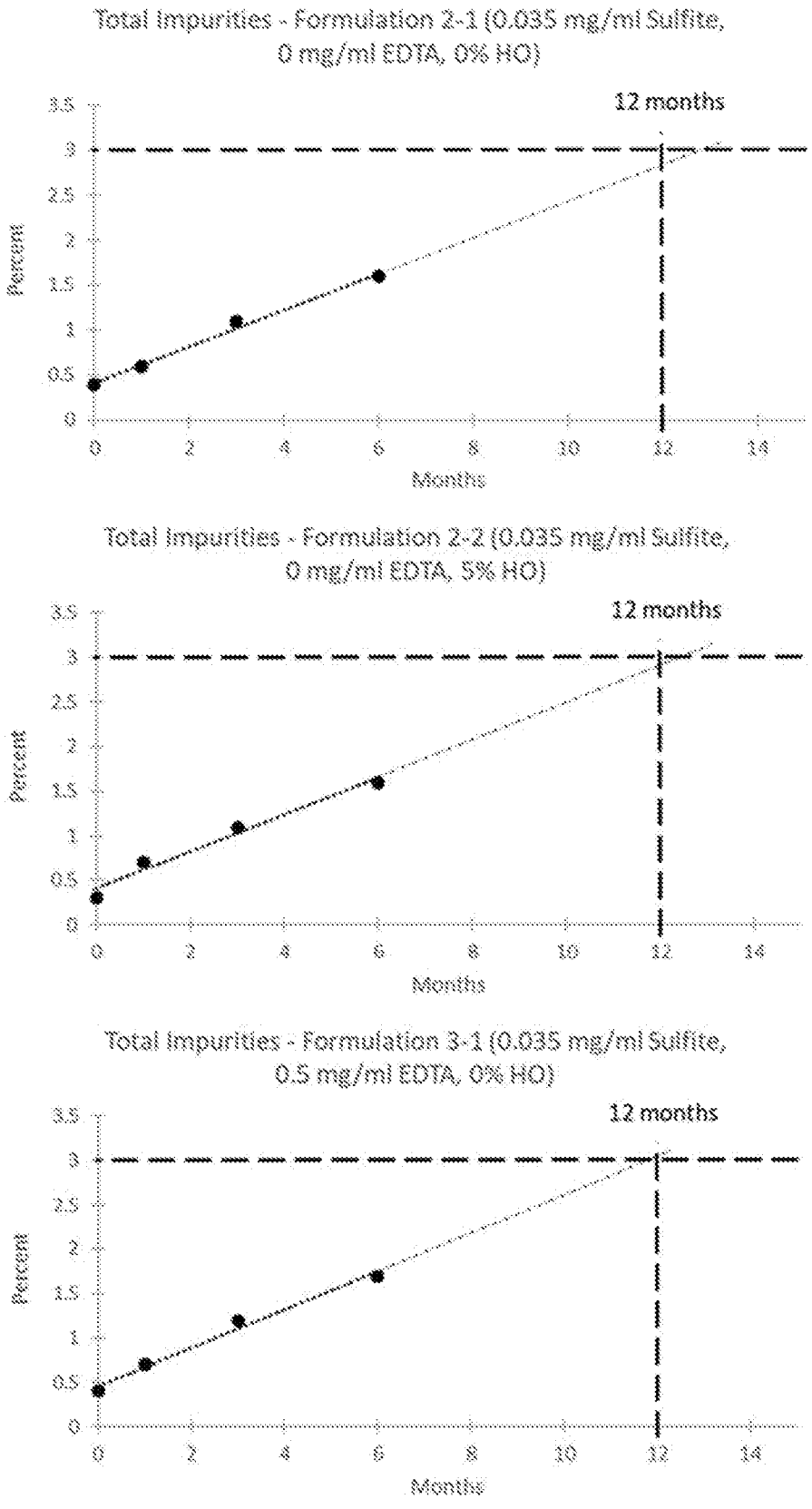
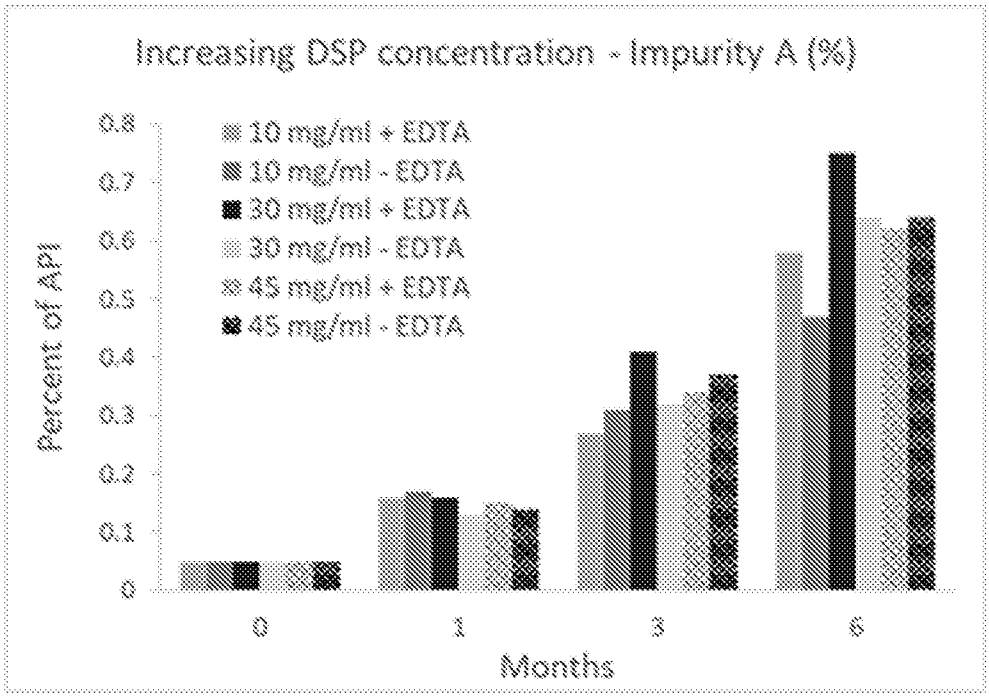

Total Impurities - Formulation 2-1 (0.035 mg/ml Sulfite, 0 mg/ml EDTA, 0% HO)
12 months
Percent
Months
Total Impurities - Formulation 2-2 (0.035 mg/ml Sulfite, 0 mg/ml EDTA, 5% HO)
12 months
Percent
Months
Total Impurities - Formulation 3-1 (0.035 mg/ml Sulfite, 0.5 mg/ml EDTA, 0% HO)
12 months
Percent
Months

Figure 45


Increasing DSP concentration - Impurity A (%)
Percent of API
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
10 mg/ml + EDTA
10 mg/ml - EDTA
30 mg/ml + EDTA
30 mg/ml - EDTA
45 mg/ml + EDTA
45 mg/ml - EDTA
0
1
3
6
Months

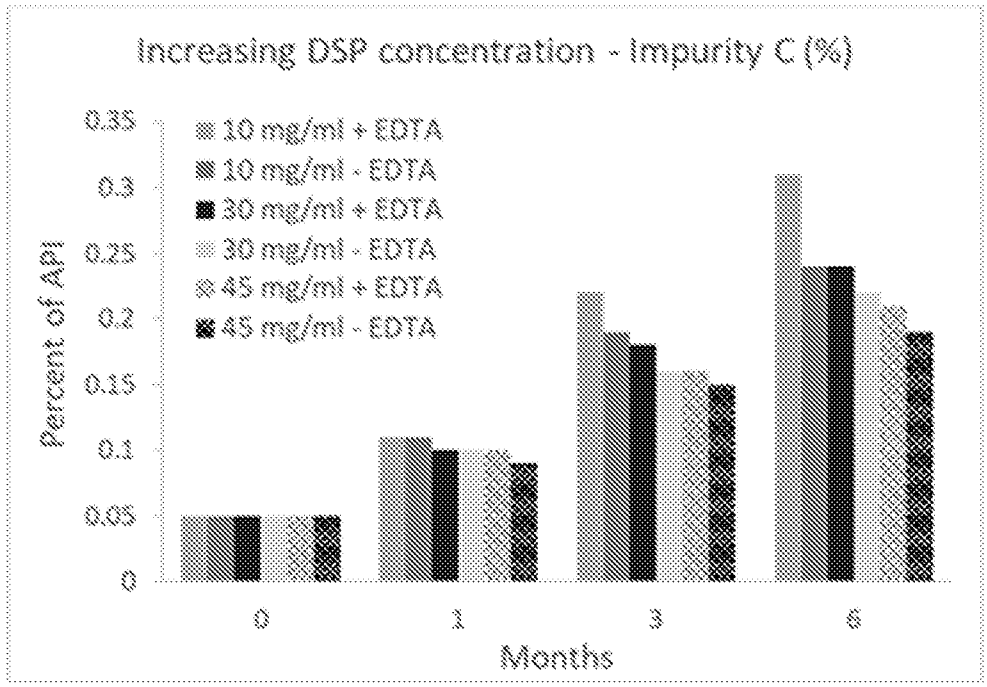
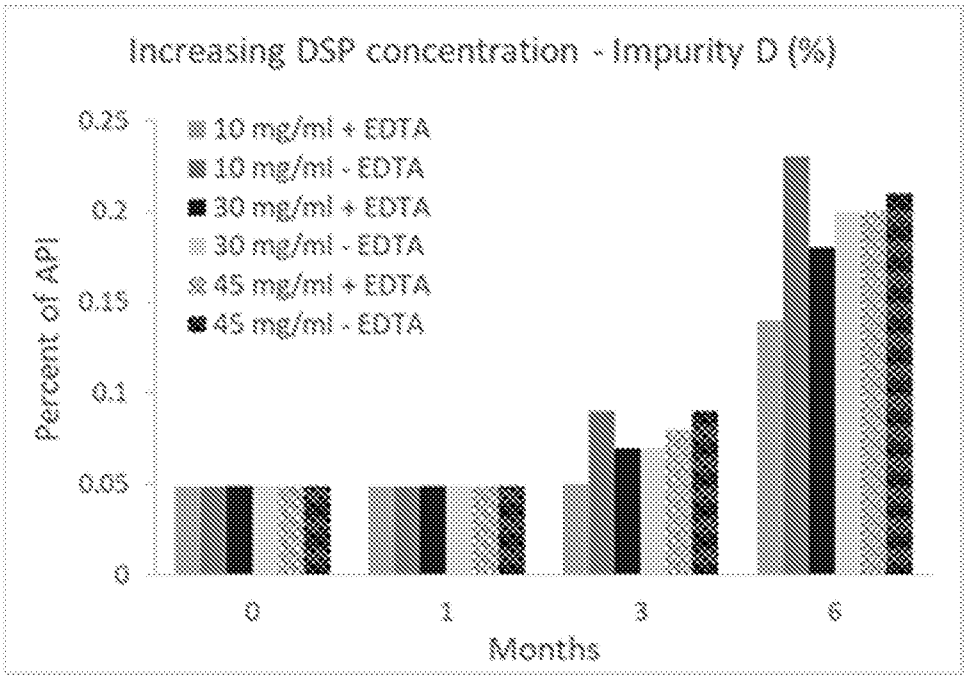

Increasing DSP concentration - Impurity C (%)
Percent of API
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
10 mg/ml + EDTA
10 mg/ml - EDTA
30 mg/ml + EDTA
30 mg/ml - EDTA
45 mg/ml + EDTA
45 mg/ml - EDTA
0
1
3
6
Months

Figure 46


Increasing DSP concentration - Impurity D (%)
10 mg/ml + EDTA
10 mg/ml - EDTA
30 mg/ml + EDTA
30 mg/ml - EDTA
45 mg/ml + EDTA
45 mg/ml - EDTA
Percent of API
0.25
0.2
0.15
0.1
0.05
0
0
1
3
6
Months

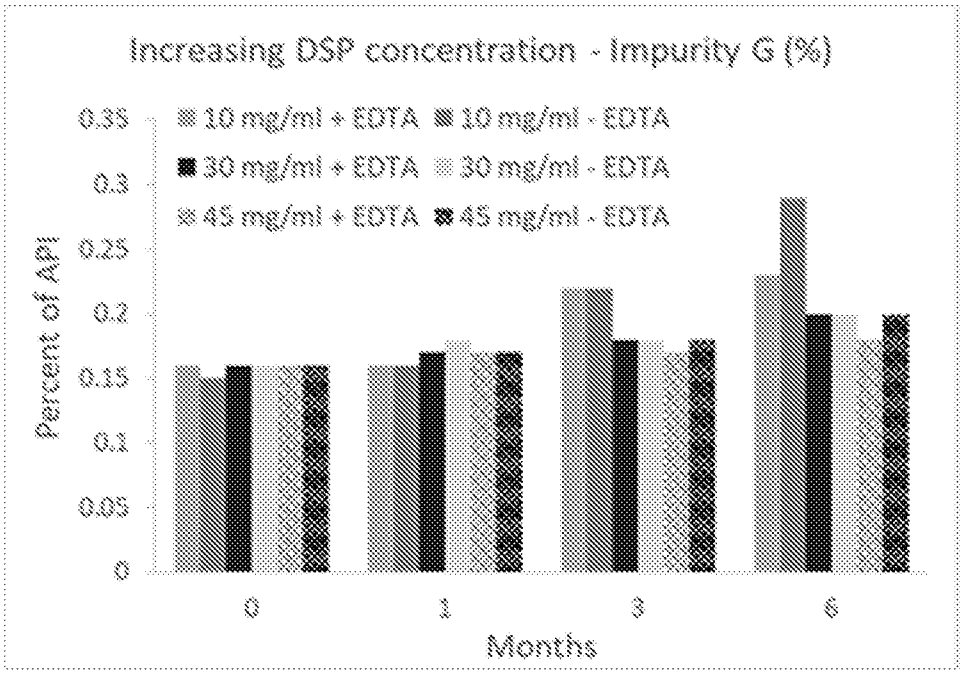
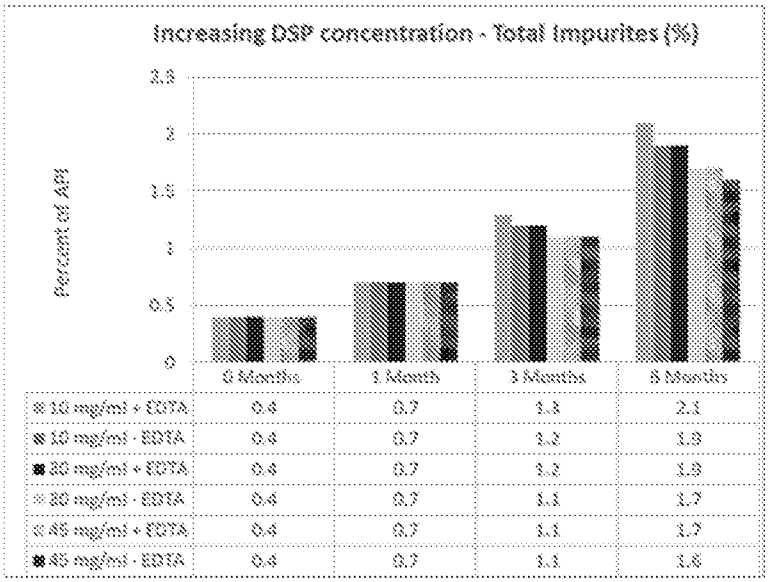

Increasing DSP concentration - Impurity G (%)
10 mg/ml + EDTA
10 mg/ml - EDTA
30 mg/ml + EDTA
30 mg/ml - EDTA
45 mg/ml + EDTA
45 mg/ml - EDTA
Percent of API
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
1
3
6
Months

Figure 47



	0 Months	1 Month	3 Months	6 Months
10 mg/ml + EDTA	0.4	0.7	1.3	2.1
10 mg/ml - EDTA	0.4	0.7	1.2	1.9
30 mg/ml + EDTA	0.4	0.7	1.2	1.9
30 mg/ml - EDTA	0.4	0.7	1.1	1.7
45 mg/ml + EDTA	0.4	0.7	1.1	1.7
45 mg/ml - EDTA	0.4	0.7	1.1	1.6