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February 11, 2013

VIA FED EX

Division of Docket Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fisher Lane, Room 1061
Rockville, MD 20852

ANDA Suitability Petition

Dear Sir or Madam,

The undersigned submits this Suitability Petition ("Petition") under Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act ("the Act"), and in accordance with 21 CFR 10.20, 10.30, and 314.93, to request that the Commissioner of the Food and Drug Administration declare new drug strengths (i.e., total drug content) of hydroxychloroquine sulfate tablets, 100, 300 and 400 mg (equivalent to 77.5, 232.5 and 310 mg base), are suitable for submission and subsequent Food and Drug Administration ("FDA") review pursuant to an abbreviated new drug application ("ANDA").

A. Action Requested

The petitioner requests that the Commissioner declare that hydroxychloroquine sulfate tablets 100, 300 and 400 mg, are suitable for submission in an ANDA.

The reference-listed drug ("RLD") is Sanofi-Aventis U.S. LLC's ("Sanofi") currently approved Plaquenil (hydroxychloroquine sulfate tablet) 200 mg (NDA 09-768), which is listed in the current edition of *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "*Orange Book*"). A copy of the NDA 09-768 Detail Record from the current electronic edition of the *Orange Book* is presented in Attachment 1.

The drug, dosage form, route of administration, dosage regimen and recommendations for use of the proposed product are the same as those of the RLD. The proposed product would differ only in strength from the marketed hydroxychloroquine sulfate tablets, 200 mg product approved under NDA 09-768. This is confirmed by a comparison of the draft label (Attachment 3) to the RLD label (Attachment 2) where the only differences are the tablet strengths.

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B. Statement of Grounds

Section 505(j)(2)(C) of the Act provides for submission of an ANDA for a new drug product that differs in strength from an RLD, provided that FDA has approved a petition seeking permission to file such an application. This Petition requests a determination from FDA that it is acceptable to submit an ANDA for a new strength of a currently approved drug product.

The new proposed strengths, 100, 300 and 400 mg, will provide practitioners and patients with convenient alternative lower and higher doses as directed by the dosing instructions for the approved hydroxychloroquine sulfate label. A summary of the rationale for the proposed tablet strengths based on labeled dosing and administration is provided in Table 1.

Table 1: Rationale for Proposed Tablet Strengths Based on Labeled Dosing and Administration

Indication	Labeled Dosing and Administration	Rationale for Proposed Tablet Strengths
Malaria (suppression)	Adults: 400 mg once weekly Infants and children: 5 mg base/kg once weekly If circumstances permit, suppressive therapy should begin two weeks prior to exposure. However, failing this, in adults an initial double (loading) dose of 800 mg (equal to 620 mg base), or in children 10 mg base/kg may be taken in two divided doses, six hours apart. The suppressive therapy should be continued for eight weeks after leaving the endemic area.	**100 mg tablet:** Provides practitioners the ability to prescribe a lower dose for smaller children based on 5 mg/kg weekly regimen (e.g., ~15.5 kg child). **300 mg tablet:** Provides an intermediate dose between 200 and 400 mg for pediatrics requiring initial double loading on a 10 mg base/kg basis (e.g., ~25 kg child). **400 mg tablet:** Provides patient convenience in cases where initial double loading (800 mg) is indicated for adults (i.e., two 400 mg tablets versus four 200 mg tablets).
Malaria (acute attack)	Adults: Initial dose of 800 mg followed by 400 mg in six to eight hours and 400 mg on each of two consecutive days (total of 2 g hydroxychloroquine sulfate or 1.55g base). An alternative method, employing a single dose of 800 mg, has also proven effective. The dosage for adults may also be calculated on the basis of body weight; this method is preferred for infants and children. A total dose representing 25 mg of base per kg of body weight is administered in three days, as follows: First dose: 10 mg base/kg (but not exceeding a single dose of 620 mg base) Second dose: 5 mg base/kg (but not exceeding a single dose of 310 mg base) 6 hours after first dose Third dose: 5 mg base/kg 18 hours after second dose Fourth dose: 5 mg base/kg 24 hours after third dose	**400 mg tablet:** Provides patient convenience in cases where initial double loading (800 mg) is indicated for adults (i.e., two 400 mg tablets versus four 200 mg tablets). **100, 300 and 400 mg tablets:** All three tablets provide practitioners more flexibility when dosing on a 5 or 10 mg base/kg basis.

Indication	Labeled Dosing and Administration	Rationale for Proposed Tablet Strengths
Lupus	Initially, the average adult dose is 400 mg (equal to 310 mg base) once or twice daily. This may be continued for several weeks or months, depending on the response of the patient. For prolonged maintenance therapy, a smaller dose, from 200 to 400 mg daily will frequently suffice.	**300 mg tablet:** Intermediate tablet strength for prolonged maintenance dosing "between 200 to 400 mg." **400 mg tablet:** Provides patient convenience in cases for the initial or prolonged maintenance adult dose (400 mg) is indicated (i.e., one 400 mg tablet versus two 200 mg tablets).
Rheumatoid arthritis	Adults (initial dosing): 400 to 600 mg (equal to 310 to 465 mg base) daily. Later (usually from five to ten days), the dose may gradually be increased to the optimum response level, often without return of side effects. Adult (maintenance): When a good response is obtained (usually in four to twelve weeks), the dosage is reduced by 50 percent and continued at a usual maintenance level of 200 mg to 400 mg (=155 mg to 310 mg base) daily.	**300 mg tablet:** Provides patient convenience for 600 mg dosing (i.e., two 300 mg tablets versus three 200 mg tablets) as well as convenience to reduce starting dose (600 mg) by 50 percent during the continued maintenance as per label. **400 mg tablet:** Provides patient convenience for 400 mg dosing (i.e., one 400 mg tablet versus two 200 mg tablets).

The requested change in strength should not raise any questions regarding safety or efficacy as the proposed strengths for hydroxychloroquine sulfate Tablets (i .e. 100, 300, and 400 mg) represent lower and intermediate to the highest strengths between the already approved lowest (e.g., 5 mg/kg equivalent to 100 mg for a child weighing 20 kg) and the highest (800 mg) dosage regimen recommended for Plaquenil (hydroxychloroquine sulfate) and can be utilized to deliver the specific doses outlined in the RLD package insert.

Pediatric Assessment

In September 2007, Congress reauthorized the Pediatric Research Equity Act of 2003 ("PREA") that amended the Act to provide the Agency authority to require drug firms to study drugs in pediatric patients, if the Agency concludes that such studies would provide beneficial health data for the patient population. The Act specifically requires that a request be issued for a new active ingredient, a new indication, a new dosage form, a new dosing regimen or a new route of administration. This Suitability Petition is seeking approval for a drug product in additional strengths so that it is more convenient to dose patients in accordance with previously approved dosing regimens (both adult and pediatric). Because we are not seeking a determination that it is acceptable to file an

ANDA for a new active ingredient, a new indication, a new dosage form, a new dosing regimen or a new route of administration, in our view, PREA is not applicable.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

D. Economic Impact Statement

In accordance with 21 CFR 10.30(b), the petitioner will, upon the request by the Commissioner, submit economic impact information.

E. Certification

The undersigned certifies that, to his best knowledge and belief, this Petition includes all information and view on which the Petition relies, and it includes representative data and information known to the Petitioner, which are favorable to the Petition.

Sincerely,

Kip Vought, Vice President
Regulatory Affairs and Strategic Development

Attachments:

Attachment 1: Hydroxychlorquine sulfate tablets RLD *Orange Book* listing

Attachment 2: Hydroxychloroquine sulfate tablets RLD label

Attachment 3: Hydroxychloroquine sulfate tablets draft label

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