CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214581Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality

New Drug Application (NDA) 214581
Resubmission

Integrated Quality Assessment

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 214581
Assessment #2

Drug Product Name	Hydroxychloroquine tablets
Dosage Form	tablets
Strength	200 and 300 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Novitium Pharma LLC
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission	22-JUL-2021	Drug Product, Biopharmaceutics, Manufacturing/Facilities
Amendment	08-OCT-2021	Biopharmaceutics
Amendment	12-NOV-2021	Biopharmaceutics & Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	N/A	
Drug Product	Craig Bertha	Wendy Wilson-Lee
Manufacturing	Vickey He	Yong Hu
Microbiology	Vickey He	Yong Hu
Biopharmaceutics	Hansong Chen	Okpo Eradiri
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Craig Bertha	
Laboratory (OTR)	N/A	
Environmental	N/A	

TABLE OF CONTENTS

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

N/A – The application is recommended for approval.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Proposed Indication(s) including Intended Patient Population	Treatment of uncomplicated malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax;* Treatment of chronic discoid lupus erythematosus in adults; Treatment of (b) (4) rheumatoid arthritis (RA) in adults.
Duration of Treatment	Malaria: Once weekly and then for 4 weeks after leaving endemic area; Lupus and RA: chronic
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Product: Adequate

The recommendation for the drug product section from the initial review of the NDA was that it was adequate. However, a complete response letter of 12-FEB-2021 was issued for the NDA and the main quality related deficiency (b) (4) (b) (4). As a result, a scientific bridge was not established to the listed drug, Plaquenil (NDA 009768). The complete response letter also included an additional non-approvability recommendation from the biopharmaceutics team requesting that the applicant adopt the standard dissolution method in the 2018 FDA guidance for highly soluble drugs.[1] In response, the applicant

[1] Note that the first IQA had included the requested change to the dissolution method as a CR deficiency and did not list that as a non-approvability issue. In addition there was a second CR deficiency asking the applicant to tighten the dissolution acceptance criteria to Q = (b) (4)% in 30 minutes (from Q = (b) (4)% in (b) (4) minutes). During finalization of the CR letter on 29-JAN-2021, the biopharmaceutics team deleted the second comment and the first comment was downgraded to an additional non-approvability comment. However, the biopharmaceutics team recently issued an IR letter of 05-NOV-2021 asking the applicant to revise the dissolution acceptance criterion from "Q = (b) (4)% in (b) (4) minutes" to "Q = (b) (4)% in 30 minutes." The 12-NOV-2021 amendment provides the requested revision to the specification applied at release and for stability samples.

has chosen the Paddle Method with USP apparatus II. Thus, the dissolution medium has changed (b) (4) (b) (4) (b) (4). The applicant has provided a new method and validation report and these have been evaluated in this review and are deemed adequate. The new method differs from the dissolution method in the USP monograph for Hydroxychloroquine Sulfate Tablets.

The container closure systems for the two strengths of the drug product are typical HDPE bottles with child-resistant closures and induction heat seals, (b) (4) As indicated in the first IQA, the 200 mg strength drug product (both bottle counts) and the 300 mg strength product (100 ct only) were not observed to have any trends for stability parameters under both accelerated and long term conditions for 6 months, although there was some variability in the LOD results for some of the batches. The resubmission of 22-JUL-2021 does not include any updated stability data, however, the applicant submitted updated 25°C/60%RH long term stability data for 24 months for all six registration batches (three from each strength) in the 12-NOV-2021 amendment. The applicant had stated in the original submission that when updated data would be available, they would revise the expiry period to 24 months. The updated stability data are evaluated below and as a result, an **expiration dating period of 24 months is deemed acceptable**.

Labeling: Adequate

There were two minor labeling deficiencies identified in the original IQA and these were not included in the CR letter of 12-FEB-2021:

1. Modify the free-base equivalence for the 300 mg strength tablet to 232 mg from (b) (4) mg.

2. Revise the highlights section to include the route of administration and the fact that the higher strength tablet is functionally scored.

These labeling comments will be forwarded to the applicant at the time of labeling negotiations with the DRTM. Additionally, due to the revisions to the dissolution method and acceptance criterion, as compared to the USP monograph for hydroxychloroquine sulfate tablets, the applicant will be asked that these differences be indicated in both the DESCRIPTION section of the package insert as well as on the bottle labels (there are no

carton labels). In addition, [redacted] should be removed from all labeling.

Manufacturing: Adequate

The Overall Manufacturing Inspection Recommendation is **Approve**. There were no process and facility changes, thus no additional evaluation of the manufacturing process and associated controls was necessary.

Biopharmaceutics: Adequate

In the original submission, the [redacted] Biopharmaceutics team found major deficiencies [redacted] In this resubmission, the Applicant [redacted] conducted BE studies to bridge their proposed drug product and the listed drug, and requested a biowaiver for the higher strength-300 mg (refer to the review from the clinical pharmacology team).

This Biopharmaceutics review focused on the dissolution method, dissolution data, and acceptance criterion as well as the biowaiver for 300 mg strength. The following dissolution method and acceptance criterion are recommended for approval:

USP Apparatus	Speed (RPMs)	Medium/ Temperature	Volume (mL)	Sampling Times	Acceptance criterion
USP Apparatus II (paddle)	50 rpm	[redacted] 37 ± 0.5°C	500 mL	5, 10, 15, 20, 30, and 45 minutes	Q= [redacted]% in 30 minutes

In addition, the biowaiver of 300 mg strength is granted based on the supporting data.

Microbiology (if applicable): Choose an item.

N/A

List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

N/A

2. Drug Substance Deficiencies

N/A

3. Drug Product Deficiencies

N/A

4. Labeling Deficiencies

1. Modify the free-base equivalence for the 300 mg strength tablet to 232 mg from (b) (4) mg.
2. Revise the highlights section to include the route of administration and the fact that the higher strength tablet is functionally scored.

In addition, since the dissolution method and acceptance criterion are not consistent with the USP monograph for Hydroxychloroquine Sulfate Tablets, the applicant will be asked to include that information in both section 11 of the package insert and on the bottle labels. In addition, (b) (4) (b) (4) should be removed from all labeling.

5. Manufacturing Deficiencies

N/A

6. Biopharmaceutics Deficiencies

N/A

7. Microbiology Deficiencies

N/A

8. Other Deficiencies (Specify discipline, such as Environmental)

N/A

Application Technical Lead Name and Date: Craig M. Bertha, 14-DEC-2021

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	17-MAR-2020	
	III			Adequate		Sufficient information in application
	III			Adequate		Sufficient information in application
	III			Adequate		Sufficient information in application
	III			Adequate		Sufficient information in application
	III			Adequate		Sufficient information in application
	III			Adequate		Sufficient information in application

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
N/A		

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other				

14 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	NDA-214581-ORIG-1-RESUB-12
Assessment Cycle Number	2
Drug Product Name/ Strength	Hydroxychloroquine Sulfate Tablets, 200 mg and 300 mg
Route of Administration	Oral
Applicant Name	Novitium Pharma LLC
Therapeutic Classification/ OND Division	OII/DRTM
LD/RS Number	PLAQUENIL® (Hydroxychloroquine Sulfate) 200 mg Tablet, NDA 009768
Proposed Indication	The (b) (4) treatment of (b) (4) malaria due to Plasmodium vivax, P. malariae, P. ovale, and (b) (4) P. falciparum. It is also indicated for the treatment of discoid and systemic lupus erythematosus.

Assessment Recommendation: **Adequate**

Assessment Summary:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
N/A	Low	Hydroxychloroquine Sulfate is a highly soluble drug.	Low	Its initial biopharmaceutics risk is low.

Novitium Pharma LLC developed Hydroxychloroquine Sulfate Tablets, 200 mg and 300 mg and submitted the original application under NDA 214581 to seek approval from the Agency through the 505(b)(2) regulatory pathways on 4/15/2020. The Listed Drug is PLAQUENIL® (Hydroxychloroquine Sulfate) 200 mg Tablets, approved under NDA N009768 and held by Concordia Pharmaceuticals Inc. The proposed indication is for the (b) (4) treatment of (b) (4) malaria due to Plasmodium vivax, P. malariae, P. ovale, and (b) (4) P. falciparum. It is also indicated for the treatment of discoid and systemic lupus erythematosus.

In the original submission, (b) (4) (b) (4), the Biopharmaceutics team found some major deficiencies (b) (4) during last review cycle, which are listed in Section "Highlight of Key Issues from Last Cycle and Their Resolution". Hence, (b) (4) the submitted data were not adequate (b) (4). On 2/12/2021, a Complete Response was issued to NDA 214581.

On 7/22/2021, the Applicant resubmitted NDA 214581. In this resubmission, the Applicant (b) (4) (b) (4) conducted BE studies to bridge their proposed drug product and the LD, and requested a biowaiver for the higher strength-300 mg.

This Biopharmaceutics review focuses on the dissolution method, dissolution data, and acceptance criterion as well as the biowaiver for 300 mg strength.

The following dissolution method and acceptance criterion have been approved:

USP Apparatus	Speed (RPMs)	Medium/ Temperature	Volume (mL)	Sampling Times	Acceptance criterion
USP Apparatus II (paddle)	50 rpm	(b) (4) 37 ± 0.5°C	500 mL	5, 10, 15, 20, 30, and 45 minutes	Q= (b) (4)% in 30 minutes

In addition, the biowaiver of 300 mg strength is granted based on the supporting data.

Recommendation and conclusion:
From a Biopharmaceutics perspective, this Reviewer concludes that NDA-214581-ORIG-1-RESUB-12 for Hydroxychloroquine Sulfate Tablets, 200 mg and 300 mg is ADEQUATE.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
e-CTD 0001/original submission	4/6/2020
e-CTD 0013/response to Biopharma IR	10/8/2021
e-CTD 0016/response to Biopharma IR	11/12/2021

Highlight of Key Issues from Last Cycle and Their Resolution:

- There were several inadequacies associated with the method suitability experiments of the model drugs.

(b) (4)

Concise Description of Outstanding Issues:

- None.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *{Adequate}*

1. Dissolution method

In the original submission, the Applicant used the following dissolution method to conduct dissolution testing:

Table 1. The originally proposed QC dissolution method

USP Apparatus	Speed (RPMs)	Medium/ Temperature	Volume (mL)	Sampling Times	Acceptance criterion
USP Apparatus II (paddle)	50 rpm	(b) (4) 37 ± 0.5°C	500 mL	(b) (4)	Q= (b) (4) % in (b) (4) minutes

The Applicant conducted dissolution testing in (b) (4), which is not accetpable. Because Hydroxychloroquine Sulfate is a highly soluble drug, the Applicant should use a standard dissolution method recommended by the 2018 FDA guidance for highly soluble drug to conduct dissolution testing. This deficiency was conveyed to the Applicant in the CR letter.

In this resubmission, the Applicant accepted our recommendation and employed the following standard method to conduct dissolution testing:

Table 2. The currently proposed QC dissolution method

USP Apparatus	Speed (RPMs)	Medium/ Temperature	Volume (mL)	Sampling Times	Acceptance criterion

USP Apparatus II (paddle)	50 rpm	0.1 N HCl, 37 ± 0.5°C	500 mL	5, 10, 15, 20, 30, and 45 minutes	Q=(b)(4)% in (b)(4) minutes

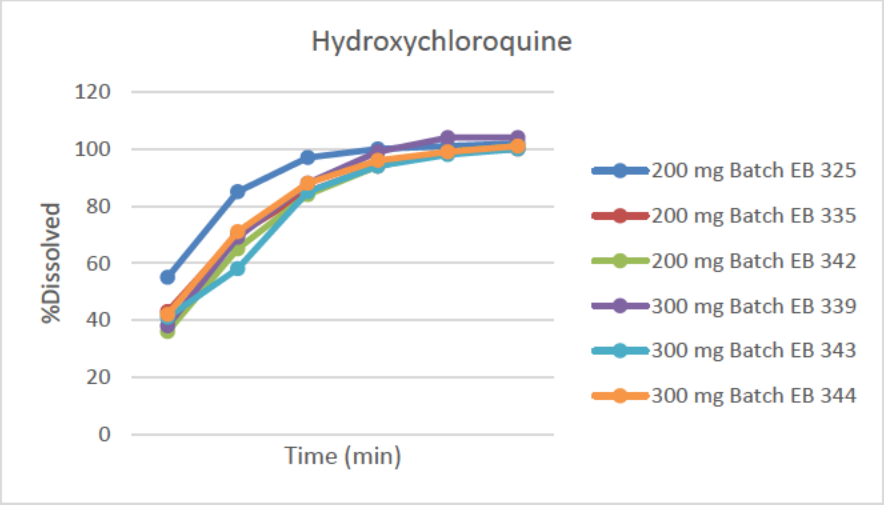
Table 3. Mean dissolution data in 0.1 N HCl (500 mL, paddle at 50 rpm)

Batch number/time (min)	5	10	15	20	30	45
200 mg Batch EB 325	55	85	97	100	101	102
200 mg Batch EB 335	43	70	85	94	99	100
200 mg Batch EB 342	36	65	84	94	99	101
300 mg Batch EB 339	38	69	88	99	104	104
300 mg Batch EB 343	41	58	85	94	98	100
300 mg Batch EB 344	42	71	88	96	99	101

Reviewer's comment:

The Applicant provided the dissolution data in 500 mL of 0.1 N HCl with paddle at 50 rpm (a standard dissolution condition recommended by 2018 FDA guidance) for three batches per strength. The data show that the proposed drug product demonstrates rapid dissolution, i.e., >85% in 30 minutes. However, they proposed "Q=(b)(4)% in (b)(4)minutes" as the acceptance criterion, which is not acceptable. Per the 2018 FDA guidance, the Applicant should also set the standard dissolution acceptance criterion (i.e., Q=(b)(4)% in 30 minutes). This deficiency was conveyed to the Applicant in Biopharmaceutics IR 2 (see Appendix for details).

Figure 1. Mean dissolution profile comparison of 200 mg and 300 mg strengths



2. Dissolution acceptance criterion

In the response to Biopharmaceutics IR 2, the Applicant accepted our recommendation and revised the dissolution acceptance criterion from "Q=(b)(4)% in (b)(4) minutes" to "Q=(b)(4)% in 30 minutes".

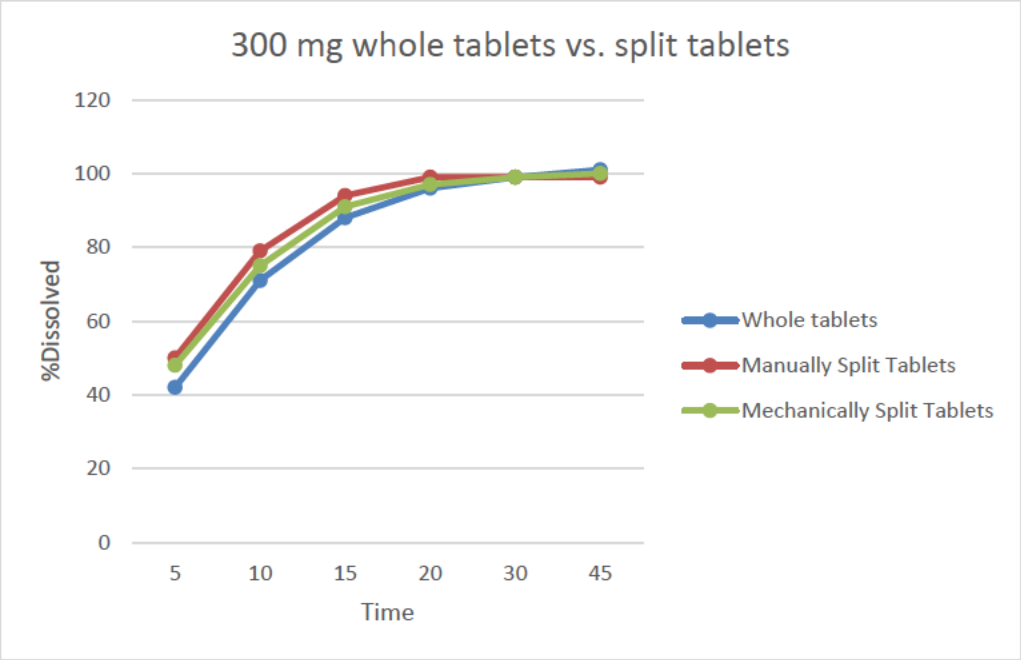
3. Split tablets

Hydroxychloroquine 300 mg tablets have functional score. In this resubmission, the Applicant provided the dissolution data of 300 mg split tablets.

Table 4. Mean dissolution comparison of whole and half tablets, 300 mg Batch EB 344

Time points (min)	5	10	15	20	30	45
Whole tablets	42	71	88	96	99	101
Manually Split Tablets	50	79	94	99	99	99
Mechanically Split Tablets	48	75	91	97	99	100

Figure 2. Mean dissolution profile comparison of 300 mg Batch EB 344 whole tablets and split tablets



The comparative dissolution data show that 300 mg Batch EB 344 whole tablets and split tablets have similar dissolution profiles because all of them have more than 85% of dissolution within 15 minutes. The individual data of half tablets show that manually and mechanically split tablets meet the acceptance criterion "Q=(b)(4)% in 30 minutes".

B. 13 BIOWAIVER REQUEST

Assessment: *{Adequate}*

The Applicant proposed 300 mg strength in the submission. However, the Applicant did not request an official biowaiver request for this strength in this resubmission. As previously stated under PIND 143564, we recommended that a waiver of in vivo study requirements may be considered for the proposed 300 mg strength based on the following:

1) A biowaiver request is included in this resubmission
2) Acceptable BA studies on the 200 mg strength
3) Evidence of linear pharmacokinetics of hydroxychloroquine over the therapeutic dose range
4) The 300 mg and 200 mg strengths are proportionally similar in the active and inactive ingredients
5) The same in vitro dissolution procedures are used for both the 200 and 300 mg strengths, and similar dissolution results are obtained based on similarity factor (f2) calculations
6) Clinical safety and/or efficacy data on the 300 mg strength
7) Rationale for the medical necessity for the 300 mg strength.

In Biopharmaceutics IR 1 (see Appendix for details), we reiterated the above recommendations for the biowaiver of 300 mg strength. In the response to IR 2, the Applicant officially requested a biowaiver for 300 mg strength with supporting data.

BE studies between the LD and proposed drug

The Applicant conducted two BE studies (fasting and fed) to compare PLAQUENIL® (Hydroxychloroquine Sulfate) 200 mg Tablets and the proposed Hydroxychloroquine Sulfate 200 mg Tablets. Those two BE studies are acceptable per the Clinical Pharmacology Reviewer-Dr. Qianni Wu.

Evidence of linear pharmacokinetics of hydroxychloroquine over the therapeutic dose range

Initially, the Applicant did not submit any direct evidence to show that the proposed hydroxychloroquine tables' pharmacokinetics are linear. Instead, they cited the labeling of Plaquenil to claim that hydroxychloroquine's PK is linear. However, the labeling just reported that IV hydroxychloroquine has linear PK. We did not find/have information/data to extrapolate IV linear PK to oral linear PK.

After discussing this issue with the Clinical Pharmacology Team, a Clinical Pharmacology IR was sent out to request the supporting data for the PK linearity of hydroxychloroquine tables. After thoroughly reviewing the literature and other supporting data presented in the response to the IR, Dr. Qianni Qu - the clinical pharmacology Reviewer concluded that the PK linearity is demonstrated by the supporting data.

In addition, in ANDA 213342 S01, Accord Healthcare Inc. proposed three new strengths (i.e., 100 mg, 300 mg, and 400 mg) for Hydroxychloroquine Sulfate Tablets after an ANDA suitability petition for the addition of these three strengths was approved. To support the approval of these three strengths, the Applicant conducted BE studies on Hydroxychloroquine Sulfate Tablets, USP, 400 mg (1 x 400 mg) vs Plaquenil® (hydroxychloroquine sulfate) Tablets, 200 mg (x2 tablets). The BE study results additionally support the PK linearity of Hydroxychloroquine Sulfate Tablets per Dr. Qianni Wu.

Compositional proportionality of 300 mg and 200 mg strengths

Ingredients	Functions	200 mg		300 mg	
		Unit Qty mg/tablets	%w/w	Unit Qty mg/tablets	%w/w
Hydroxychloroquine Sulfate	API	200	(b) (4)	300.00	(b) (4)
Lactose Monohydrate	(b) (4)				
Corn starch,	(b) (4)				
Croscarmellose sodium,	(b) (4)				
Sucralose,	(b) (4)				
Hypromellose	(b) (4)				
Magnesium Stearate,	(b) (4)				
Talc	(b) (4)				
Polyethylene Glycol	(b) (4)				
Titanium Dioxide,	(b) (4)				
Triacetin,	(b) (4)				
Sucralose	(b) (4)				
Polysorbate 80,	(b) (4)				
Water	(b) (4)				
Total weight of coated tablets		(b) (4)	100.00	(b) (4)	100.00

The above table shows that two strengths' formulations are compositionally proportional.

Similar dissolution results between two strengths

Figure 3. Mean dissolution profile comparison of 200 mg Biobatch and 300 mg strength

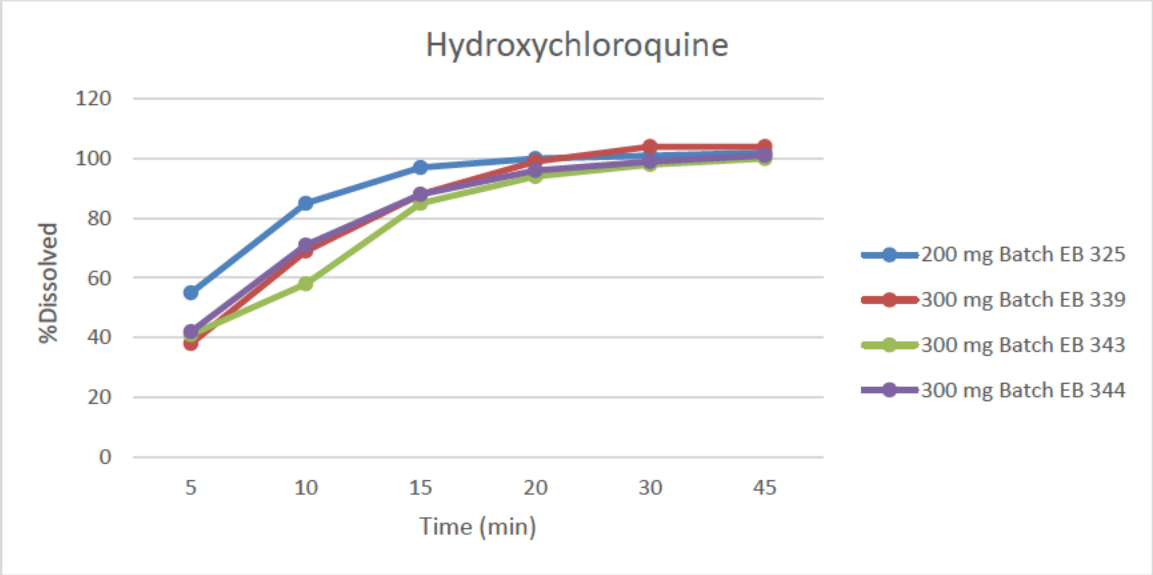


Table 2 and Figure 3 show that all three batches of 300 strength and 200 mg Biobatch EB325 have similar dissolution profiles.

Clinical safety and/or efficacy data on the 300 mg strength

Hydroxychloroquine Sulfate Tablets are indicated for the treatment of malaria, lupus erythematosus, and rheumatoid arthritis. For all of three indications, the dose taken could be more than 300 mg up to 800 mg per the labeling of Plaquenil®. Therefore, the proposed 300 mg strength does not bring any additional safety and/or efficacy concerns.

Rationale for the medical necessity for the 300 mg strength

In the response to Biopharm IR 1, the Applicant stated that 300 mg strength is medically needed because 13% of the patients are reported to take 300 mg/day via alternate-day dosing (400 mg/200 mg) or splitting tablets (1.5×200 mg tablets) per a survey. Per the labeling of Plaquenil® (hydroxychloroquine sulfate) Tablets, 200 mg, patients could take up to (b) (4) mg of dosage to treat malaria and rheumatoid arthritis. The addition of 300 mg strength will be more convenient for patients to titrate dose and reduce pill burden.

In summary, the Applicant provided sufficient supporting data for the biowaiver of 300 mg strength. Hence, the biowaiver can be granted.

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: *N/A*

Post-Approval Commitments

Assessment: *N/A*

Lifecycle Management Considerations

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

Appendix

Biopharmaceutics IR 1

You proposed a 300 mg strength which is currently unapproved in the United States and your Application does not contain in vivo bioavailability data on the new strength or a biowaiver request. As previously stated under PIND 143564, a waiver of in vivo study requirements may be considered for the proposed 300 mg strength based on the following:

1) A biowaiver request is included in the NDA
2) Acceptable BA studies on the 200 mg strength.
3) Evidence of linear pharmacokinetics of hydroxychloroquine over the therapeutic dose range.
4) The 300 mg and 200 mg strengths are proportionally similar in the active and inactive ingredients
5) The same in vitro dissolution procedures are used for both the 200 and 300 mg strengths, and similar dissolution results are obtained based on similarity factor (f2) calculations;
6) Clinical safety and/or efficacy data on the 300 mg strength
7) Rationale for the medical necessity for the 300 mg strength.

Submit a biowaiver request for the 300 mg strength as an amendment to the NDA with data and information as outlined above by October 12, 2021.

Applicant's response

The Applicant provided a response, which was assessed in this review.

Biopharmaceutics IR 2

Your proposed dissolution acceptance criterion " Q= (b)(4)% in (b)(4) minutes" is not accetpable. The FDA guidance for Industry titled "Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances" establishes standard dissolution methodology and acceptance criteria to facilitate development and evaluation for drug products that meet the conditions outlined. You have Implemented a standardized dissolution testing for your proposed drug product; however, you should also set the standard acceptance criterion (i.e., Q= (b)(4)% in 30 minutes) for quality control of your proposed drug product following the Guidance recommendations. Update relevant sections of your submission and drug product specification tables for release and stability accordingly.

Applicant's response

The Applicant accepted our recommendation and revised the dissolution acceptance criterion from "Q= (b)(4)% in (b)(4)minutes" to "Q= (b)(4)% in 30 minutes".

Primary Biopharmaceutics Assessor's Name and Date:
Hansong Chen PharmD, Ph.D.
Division of Biopharmaceutics/ONDP/OPQ

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Okpo Eradiri, Ph.D.
Division of Biopharmaceutics/ONDP/OPQ

Hansong Chen

Digitally signed by Hansong Chen
Date: 12/13/2021 10:33:52AM
GUID: 525d7d660003845a197a2e1682433d0d

Okponanabofa Eradiri

Digitally signed by Okponanabofa Eradiri
Date: 12/13/2021 11:31:49AM
GUID: 50bdfe8d00003559ede66be3fd299f65

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CRAIG M BERTHA
12/14/2021 11:46:36 AM

Office of Pharmaceutical Quality

New Drug Application (NDA) 214581

Integrated Quality Assessment

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 214581
Assessment #1

Drug Product Name	Hydroxychloroquine tablets
Dosage Form	tablets
Strength	200 and 300 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Novitium Pharma LLC
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	06/15-APR-2020	All
Amendment	20-APR-2020	Biopharmaceutics
Amendment	01-MAY-2020	Drug Product (labeling)
Amendment	21-MAY-2020	Biopharmaceutics
Amendment	29-JUN-2020	Manufacturing
Amendment	08-SEP-2020	Manufacturing

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Craig Bertha	Wendy Wilson-Lee
Drug Product	Craig Bertha	Wendy Wilson-Lee
Manufacturing	Vickey He	Yong Hu
Microbiology	Vickey He	Yong Hu
Biopharmaceutics	Hansong Chen	Okpo Eradiri
Regulatory Business Process Manager	Florence Aisida	
Application Technical Lead	Craig Bertha	
Laboratory (OTR)	N/A	
Environmental	Craig Bertha	Wendy Wilson-Lee

TABLE OF CONTENTS

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

A complete response is recommended. (b) (4) (b) (4)

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Proposed Indication(s) including Intended Patient Population	Treatment of uncomplicated malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax;* Treatment of chronic discoid lupus erythematosus in adults; Treatment of (b) (4) rheumatoid arthritis (RA) in adults.
Duration of Treatment	Malaria: Once weekly and then for 4 weeks after leaving endemic area; Lupus and RA: chronic
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

Novitium obtains the Hydroxychloroquine Sulphate, USP from (b) (4). CMC information is supplied by reference to DMF (b) (4). The (b) (4) DMF (b) (4) was recently reviewed (see review dated 17-MAR-2020) in support of approved abbreviated NDAs for solid oral dosage form drug products, and was found to be adequate. Note that the acceptance specification of Novitium is the same as the release specification of (b) (4), with the exception that the former also includes the ordinary impurities test and acceptance criterion that is in the USP monograph for hydroxychloroquine sulfate. As this product is also for oral administration, no further review of DMF (b) (4) is needed. The NDA does include an assay, impurities method, a particle size distribution method, and a residual solvents method as well as validation reports. All of these methods have been evaluated (see S.4) and are found to be suitable for regulatory purposes based on the validation reports. It is not necessary to forward these methods to the Agency laboratory for assessment.

Drug Product: Adequate

The reference drug for the low strength of this drug product is Plaquenil® 200 mg tablets (NDA 009768). Hydroxychloroquine sulfate is not a new molecular entity. The applicant is obtaining the API from a source that has already been approved for other oral drug products. The immediate release coated tablets use a common formulation and the excipients are compendial grade. The applicant has requested a biowaiver from performing a comparative bioavailability study to the reference product.

The applicant has performed a risk assessment for elemental impurities. As a result, no routine testing of the drug product for any specific elemental impurities is necessary. (b) (4) (b) (4). The 300 mg tablet is scored for splitting, and the applicant has shown that split tablets had sufficient content uniformity, acceptable mass loss, and dissolution and stability was not impacted adversely.

The proposed drug product specification is acceptable and includes the parameters expected as per the recommendations of ICH Q6A. None of the drug product degradants (or process impurities from the drug substance), include structural alerts, and the applicant has followed Q3B recommendations. The analytical methods were found to be adequate for regulatory purposes and it is not necessary to forward any of these to the Agency laboratory.

The container closure systems are typical HDPE bottles with child-resistant closures and induction heat seals (b) (4). For the 200 mg strength drug product (both bottle counts) and the 300 mg strength product (100 ct only) there were no trends observed for any of the stability parameters under both accelerated and long term conditions for 6 months, although there was some variability in the LOD results for some of the batches. The acceptance criteria for LOD, assay, impurities, and microbial limits are reasonable and should allow the product to have a commercially viable expiration dating period once more data are provided. **The (b) (4) month expiration dating period proposed is acceptable**.

Labeling: Adequate

In general the labeling/labels are adequate, although during labeling negotiations, the applicant will be asked to modify the free-base equivalence for the 300 mg strength tablet to 232 mg from (b) (4)

mg. Also, the highlights section will be revised to include the route of administration and the fact that the higher strength tablet is functionally scored.

Manufacturing: Adequate

Hydroxychloroquine Sulfate 200 mg and 300 mg tablets are (b) (4) (b) (4) immediate release tablets. DS has high water solubility and two known polymorphic forms. 300 mg is a scored tablet. The 200 mg is packaged in 30 and 100 count HDPE bottles, and 300 mg is packaged in 100 count HDPE bottle. The product is designated under 505(b)(2) Regulatory Pathway.

The DP manufacturer is Novitium Pharma LLC (FEI# 3012541241), and drug substance manufacturer is (b) (4) (FEI# (b) (4)). Both have acceptable experiences and compliance status for the intended function in the application. Following review of the application and inspection documents for all proposed facilities in the application, there are no significant facility risks that would require PAI. The manufacturing and test facilities for this application are found acceptable based on previous history.

The proposed DP manufacturing process (b) (4) (b) (4) . Both 200 mg and 300 mg are capsule shaped tablets with a split line for the 300 mg. (b) (4) (b) (4). Commercial manufacturing process and equipment scale are the same as those in exhibit batches. The commercial process controls are supported by development and exhibit batch data. Consistent (b) (4) (b) (4)) results have been demonstrated on the exhibit batches for both strengths. All exhibit batches met the final product acceptance criteria. Exhibit batch data have also been provided (b) (4)

Biopharmaceutics: Inadequate

Novitium Pharma LLC developed Hydroxychloroquine Sulfate Tablets, 200 mg and 300 mg and submitted this application under NDA 214581 to seek approval from the Agency through the 505(b)(2) regulatory pathway on 4/15/2020. The Listed Drug that the Applicant relied on the findings on efficacy and safety is PLAQUENIL® (Hydroxychloroquine

Sulfate) 200 mg Tablets, approved under NDA N009768 and held by Concordia Pharmaceuticals Inc.

Initially, the Applicant conducted a bioequivalence study under fasting conditions to compare the LD and proposed drug product; however, the study failed. The Applicant reformulated their proposed drug product, but did not conduct a second BE study to compare the LD and the new formulation (b) (4)

(b) (4)

Recommendation and conclusion:
From a Biopharmaceutics perspective, this Reviewer concludes that NDA 214581 for Hydroxychloroquine Sulfate Tablets, 200 mg and 300 mg is INADEQUATE; therefore, a Complete Response is recommended for this NDA.

Microbiology (if applicable): Choose an item.

N/A

C. Risk Assessment

DP CQA	Factors that may impact the CQA	O[1]	S[1, 2]	D[1]	Initial RA FMECA RPN #	Comment & considerations for risk assessment	Final RA	Comments/Lifecycle considerations
ID	▪Incorrect elucidation of structure	1	3	1	3	(b) (4)		
Assay	▪Variable PSD for DS (b) (4) ▪Impurities in API	2	3	2	12			
Degradation Products /Purity	▪Degradation (b) (4) (b) (4) during processing ▪Assay/purity of drug substance	2	3	3	18			
Dissolution	▪Large drug substance particle size ▪Drug substance (b) (4) ▪Seal and film coating weight variation	1	3	3	9			

[1] O = Probability of Occurrence; S = Severity of Effect; D = Detectability
[2] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs (thus a median value of "3" will be used throughout)

						(b) (4)		
Uniformity of Dosage Units (content uniformity or CU)	▪Variable PSD for drug substance (b) (4)	2	3	4	24			
Microbial limits	▪Microbial limits testing part of drug product specifications (b) (4) ▪Microbial growth during processing (film coating) ▪Bioburden from components of formulation ▪No microbial limits testing proposed for drug product at release	1	3	1	3			

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

N/A

2. Drug Substance Deficiencies

N/A

3. Drug Product Deficiencies

N/A

4. Labeling Deficiencies

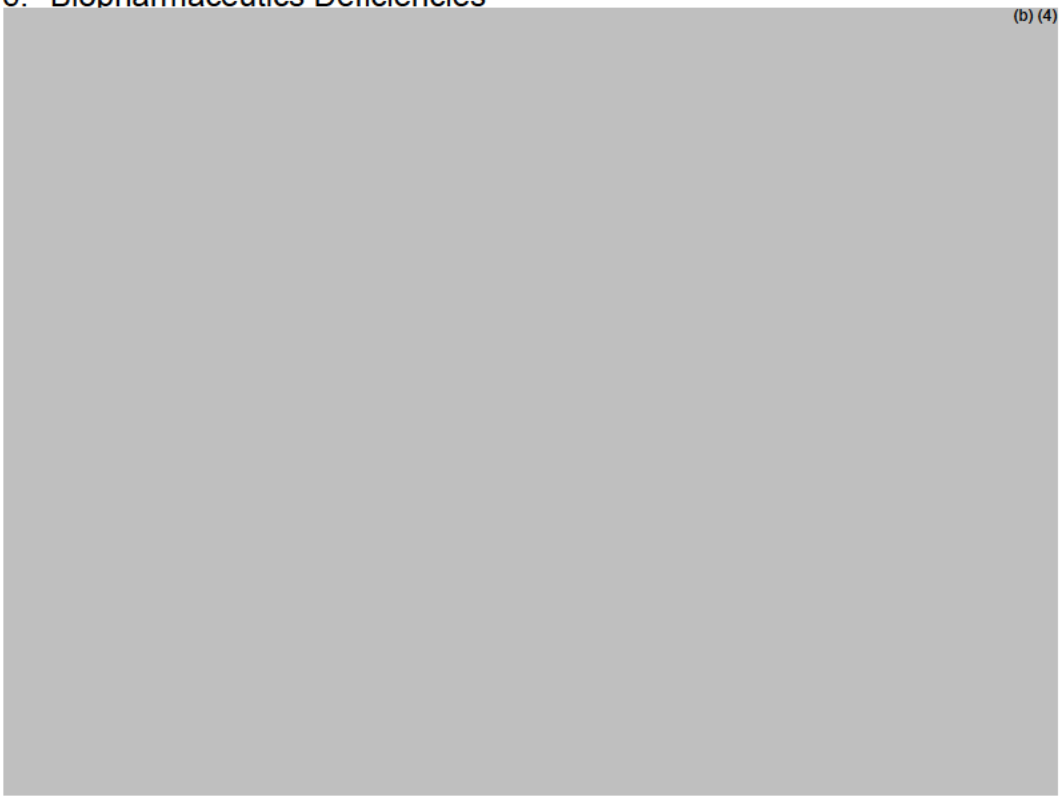
1. Modify the free-base equivalence for the 300 mg strength tablet to 232 mg from (b) (4) mg.
2. Revise the highlights section to include the route of administration and the fact that the higher strength tablet is functionally scored.

5. Manufacturing Deficiencies

N/A

6. Biopharmaceutics Deficiencies

(b) (4)



1 Page has been Withheld in Full as B4(CCI/TS) Immediately Following this Page

Dissolution

1) You used the dissolution method ((b) (4) , (b) (4) to conduct dissolution tests. Since Hydroxychloroquine Sulfate is a highly soluble drug, use a standard dissolution method recommended in the 2018 FDA guidance for highly soluble drugs to conduct dissolution testing.

2) The proposed dissolution acceptance criterion (i.e. Q= (b) (4) % in (b) (4) minutes) is permissive and not acceptable. Tighten the acceptance criterion to Q= (b) (4) % in 30 minutes.

7. Microbiology Deficiencies

N/A

8. Other Deficiencies (Specify discipline, such as Environmental)

N/A

Application Technical Lead Name and Date: Craig M. Bertha, 15-DEC-2020

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	17-MAR-2020	
	III			Adequate		Sufficient information in application
	III			Adequate		Sufficient information in application
	III			Adequate		Sufficient information in application
	III			Adequate		Sufficient information in application
	III			Adequate		Sufficient information in application
	III			Adequate		Sufficient information in application

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
N/A		

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other				

31 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	N/A	
Established name(s)	Hydroxychloroquine sulfate	Qualifies for exemption from USP salt policy
Route(s) of administration	No	PI to be revised to include "for oral use"
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	No	PI to be revised to include "functionally scored"
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Exempted	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Yes	The score of the 300 mg tablet is mentioned.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Functionally scored	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Yes	No proprietary name is proposed
Dosage form(s) and route(s) of administration	Yes	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Yes	This compound is exempt as there were monographs for HCQ sulfate and HCQ sulfate tablets before the USP salt policy was implemented.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	No	The reference drug labeling does not include such a description; no revision will be requested
Chemical name, structural formula, molecular weight	Yes	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Yes	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section (title need to be modified to include STORAGE AND HANDLING)		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
Available units (e.g., bottles of 100 tablets)	Yes	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Functionally scored	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Yes	HCQ sulfate is light sensitive and the USP monograph for the tablets indicates that the product should be dispensed in light-resistant containers.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Yes	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging	Yes	All CCSs are said to incorporate child resistant closures

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small

volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.
Please include your comments about other sections of labeling if they contain product quality information.

N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	The package insert indicates that the drug product is manufactured by: Novitium Pharma LLC 70 Lake Drive, East Windsor New Jersey 08520	This is in compliance with 21 CFR 201.1.

2.0 PATIENT LABELING

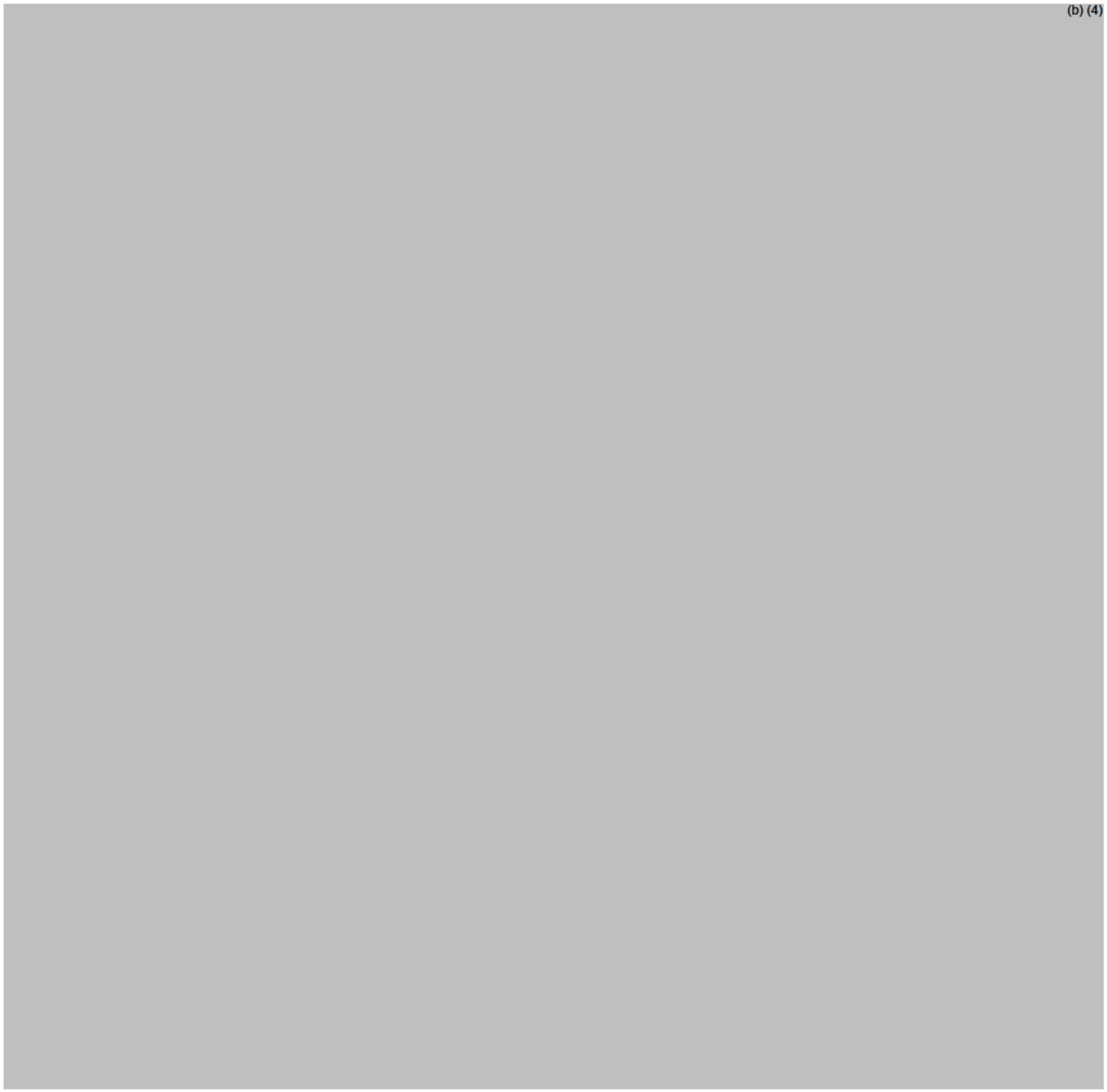
Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): N/A

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Labels

(b) (4)



3.2 Carton Labeling N/A

Item	Information Provided in the NDA	Assessor's Comments about Container Labeling
Proprietary name, established name, and dosage form (font size and prominence	Yes	No proprietary name is proposed
Dosage strength	Yes	
Route of administration	N/A – product for oral administration	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Yes, although revision is needed for the high strength	In the 29-JUN-2020 amendment, the applicant revised the labels to include the equivalency statements as per the USP salt naming guidance
Net contents (e.g. tablet count)	Yes	
"Rx only" displayed on the principal display	Yes	
NDC number	Yes	Not required by regulation 21 CFR 201.2
Lot number and expiration date	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	

Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes	

Item	Information Provided in the NDA	Assessor's Comments about Container Labeling
Name of manufacturer/distributor	Yes	
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	*N/A*	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: Adequate.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

Adequate. Note that during labeling negotiations, the applicant will be asked to modify the free-base equivalence for the 300 mg strength tablet to 232 mg from (b) (4) mg. Also, the highlights section will be revised to include the route of administration and the fact that the higher strength tablet is functionally scored.

Primary Labeling Assessor Name and Date:
Craig M. Bertha, CMC Lead for DPACC/DRTM (02-JUL-2020)

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Wendy Wilson, PhD, Division Director (actg), OPQ/ONDP/DNDPII

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Craig Bertha

Digitally signed by Craig Bertha
Date: 7/02/2020 09:39:39AM
GUID: 50841a65000098a9383c817879a6a84d

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 7/02/2020 09:45:41AM
GUID: 50816dbc000085595ca3284bbca465a8

43 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	NDA 214581
Assessment Cycle Number	1
Drug Product Name/ Strength	Hydroxychloroquine Sulfate Tablets, 200 mg and 300 mg
Route of Administration	Oral
Applicant Name	Novitium Pharma LLC
Therapeutic Classification/ OND Division	OII/DRTM
LD/RS Number	PLAQUENIL® (Hydroxychloroquine Sulfate) 200 mg Tablet, NDA 009768
Proposed Indication	The (b) (4) treatment of (b) (4) malaria due to Plasmodium vivax, P. malariae, P. ovale, and (b) (4) P. falciparum. It is also indicated for the treatment of discoid and systemic lupus erythematosus.

Assessment Recommendation: **Inadequate**

Assessment Summary:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
N/A	Low	Hydroxychloroquine Sulfate is a highly soluble drug.	Low	Its initial biopharmaceutics risk is low.

Novitium Pharma LLC developed Hydroxychloroquine Sulfate Tablets, 200 mg and 300 mg and submitted this application under NDA 214581 to seek approval from the Agency through the 505(b)(2) regulatory pathway on 4/15/2020. The Listed Drug that the Applicant relied on the findings on efficacy and safety is PLAQUENIL® (Hydroxychloroquine Sulfate) 200 mg Tablets, approved under NDA N009768 and held by Concordia Pharmaceuticals Inc. The proposed indication is for the (b) (4) treatment of (b) (4) malaria due to

Plasmodium vivax, P. malariae, P. ovale, and (b) (4) P. falciparum. It is also indicated for the treatment of discoid and systemic lupus erythematosus.

Initially, the Applicant conducted a bioequivalence study under fasting conditions to compare the LD and proposed drug product; however, the study failed. The Applicant reformulated their proposed drug product, but did not conduct a second BE study to compare the LD and the new formulation. (b) (4)

(b) (4)

Recommendation and conclusion:
From a Biopharmaceutics perspective, this Reviewer concludes that NDA 214581 for Hydroxychloroquine Sulfate Tablets, 200 mg and 300 mg is INADEQUATE; therefore, a Complete Response is recommended for this NDA.

The following information are to be conveyed to the Applicant in the CR letter:

(b) (4)

11 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

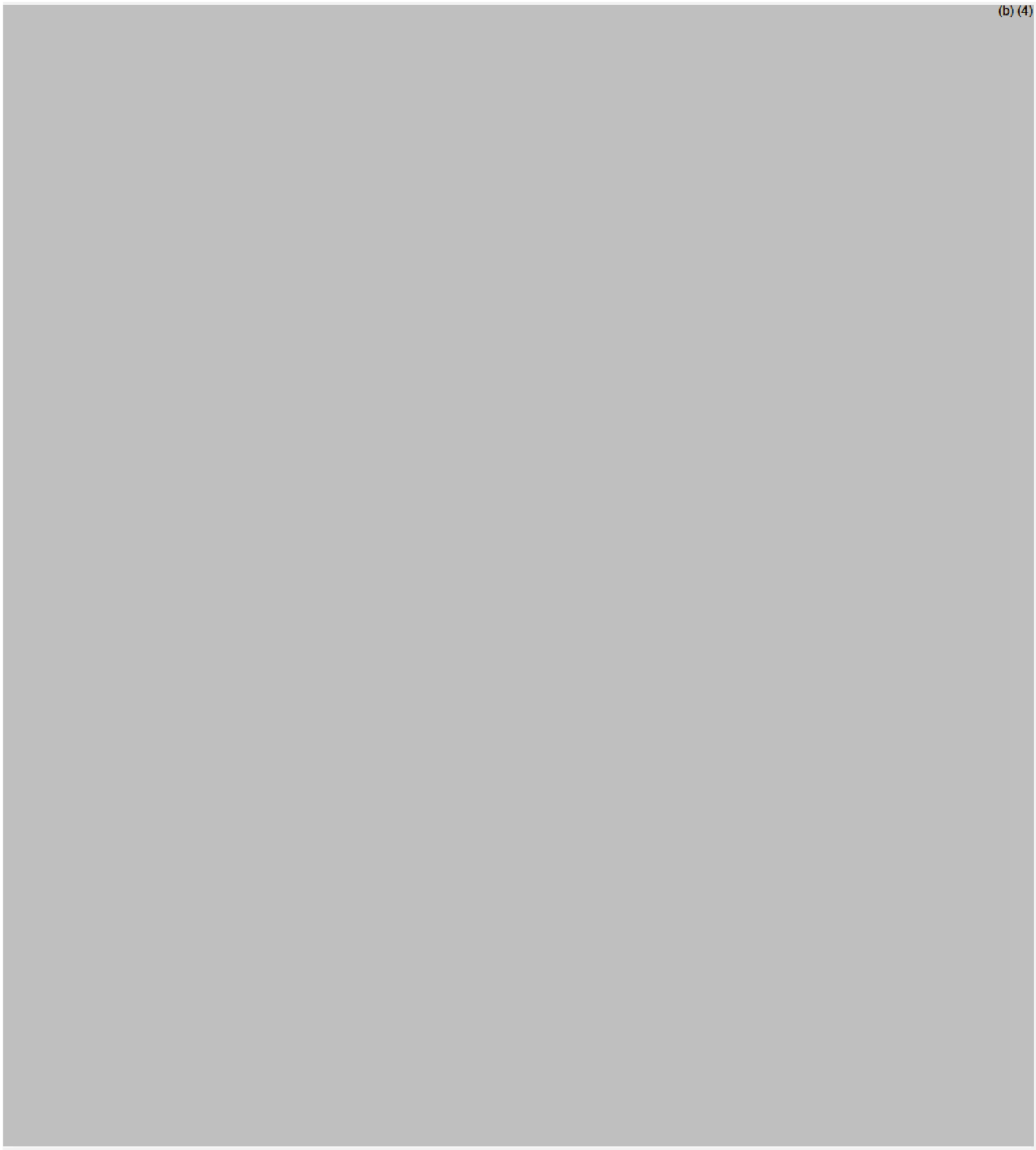
Discrepancy between the method suitability and pivotal experiments

According to the FDA BCS guidance, the study protocol for evaluating the test drug should be the same as the method suitability experiments. (b) (4)

(b) (4)

Dissolution:

The Applicant provided the dissolution data in multimedia per the FDA BCS guidance.



Reviewer's comment:

The above dissolution data show that both 300 mg and 200 mg of Hydroxychloroquine Sulfate Tablets are rapidly dissolving (i.e. more than 85% dissolution in 30 minutes) in 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer. The comparative dissolution data in multi-media also

show that proposed Hydroxychloroquine Sulfate Tablets 200 mg and 300 mg have similar dissolution profiles as those of LD in multimedia except proposed 300 mg in pH 4.5 acetate buffer, where Batch EB-339 has a dissolution of (b) (4) at 15 minutes. Because this batch's dissolution at 15 minutes is less than (b) (4), we could not determine whether it has a similar dissolution profile as LD in pH 4.5 acetate buffer without calculating a similarity factor. Furthermore, there is no enough valid time points to calculate the similarity factor because the dissolution samples were collected from 15 minutes. However, it is still acceptable considering the following reasons:

- *Hydroxychloroquine Sulfate is a highly soluble drug, the biopharmaceutics risk is low*
- *Both Batch EB-339 and LD have (b) (4) dissolution at 30 minutes.*

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *{Inadequate}*

QC Dissolution method

The Applicant used the following dissolution method to conduct dissolution testing:

Table 13. The proposed QC dissolution method

USP Apparatus	Speed (RPMs)	Medium/ Temperature	Volume (mL)	Sampling Times	Acceptance criterion
USP apparatus II (paddle)	50 rpm	(b) (4), 37 ± 0.5°C	500 mL	(b) (4)	Q= (b) (4)% in (b) (4) minutes

Reviewer's comment:

The Applicant conducted QC dissolution testing in (b) (4) which is not acceptable. Because Hydroxychloroquine Sulfate is a highly soluble drug, the Applicant should use a standard dissolution method recommended in the 2018 FDA guidance for highly soluble drug to conduct QC dissolution testing.

Table 14. Mean dissolution data in (b) (4) (paddle, 50 rpm, 500 mL)

Batch number/time (min)	15	30	45	60
300 mg Batch EB-339 in (b) (4)	79	94	96	97
200 mg Batch EB-325 in (b) (4)	87	93	94	94

Table 15. Mean dissolution data in 0.1 N HCl (paddle, 50 rpm, 500 mL)

Batch number/time (min)	15	30	45	60
300 mg Batch EB-339 in (b) (4)	89	100	103	106

200 mg Batch EB-325 in (b) (4)	99	104	104	105

Reviewer's comment:

The Applicant did provide the dissolution data in 0.1 N HCl (standard dissolution condition recommended by 2018 FDA guidance) for one batch per strength. This is not sufficient. Instead, the Applicant should provide the complete dissolution data (individual n=12/batch, mean, SD, %RSD, profiles) using a standard dissolution method for three batches/strength. In addition, the proposed dissolution acceptance criterion (i.e. Q=(b)(4)% in (b)(4)minutes) is too permissive and not acceptable. The Applicant should tighten the dissolution acceptance criterion to Q=(b)(4)% in 30 minutes.

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Assessment:

The Applicant conducted a pilot BE study under fasting conditions to compare the equivalence between the LD and proposed drug product; however, the study failed. This failed study was involved with 24 healthy human subjects. Here are the BE study results:

Pharmacokinetic Parameters	Test Geometric Mean	Reference Geometric Mean	Test/Reference Ratio	90% Confidence Interval	Power
Ln C_{max}	(b) (4)				
Ln AUC_{0-72}					

Since T/R ratios for Cmax and AUC in the above pilot study are far less than 1, the Applicant concluded that the failure reason is that the proposed drug formulation (b) (4) But, the Applicant did not conduct a second BE study to compare the LD and new formulation. Instead, they requested a BCS based biowaiver for their new formulation.

Reviewer's comment:

The failure of the above BE study indicates that Hydroxychloroquine Sulfate is a low permeability drug. (b) (4) *Consequently, the above BE study was unlikely to fail.*

B.12 BRIDGING OF FORMULATIONS

Assessment: *N/A*

B. 13 BIOWAIVER REQUEST

Assessment: *{Inadequate}*

The Applicant requested a biowaiver for 300 mg strength. However, this biowaiver could not be granted because the BCS Class I based waiver for 200 mg strength is not acceptable.

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: *N/A*

Post-Approval Commitments

Assessment: *N/A*

Lifecycle Management Considerations

BIOPHARMACEUTICS LIST OF DEFICIENCIES

(b) (4)

Applicant's response

The Applicant provided a response, which is assessed in this review.

Primary Biopharmaceutics Assessor's Name and Date:
Hansong Chen PharmD, Ph.D.
Division of Biopharmaceutics/ONDP/OPQ

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Okpo Eradiri, Ph.D.
Division of Biopharmaceutics/ONDP/OPQ

Hansong Chen

Digitally signed by Hansong Chen
Date: 12/14/2020 11:40:07AM
GUID: 525d7d660003845a197a2e1682433d0d

Okponanabofa Eradiri

Digitally signed by Okponanabofa Eradiri
Date: 12/14/2020 11:45:21AM
GUID: 50bdfe8d00003559ede66be3fd299f65

DOCUMENT HISTORY

Document History	
Author: Integrated Quality Assessment Team, and Don Henry.	
Clearance Statement: This document is sponsored by the Integrated Quality Assessment Team. Jorge Rondon (OPRO/OE), Don Henry (OPRP/OE), and the Integrated Quality Assessment Team have cleared this template for use.	This process (CDER OPQ Integrated Quality Assessment Template) will be assessed at the following intervals and changes to the work aid will be captured as needed: This process will be assessed approximately 150 days from date issued (February 1, 2019).
Version	**Summary of Changes** **Date Issued**
04	Content update 01/17/2017
05	10/15/2017 GDUFA II Drop-down option added
06	1/3/2019 1. The Previous template and assessment guide contained information relevant to both ANDA and NDA. The document is now separated into two documents for each application type. 2. Replaced distinct Process and Facilities chapters with the new integrated Manufacturing chapter. 3. Made content updates to NDA Labeling chapter. 4. Added Maximum Daily Dose (MDD) field.

Craig Bertha

Digitally signed by Craig Bertha
Date: 12/15/2020 09:39:49AM
GUID: 50841a65000098a9383c817879a6a84d

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CRAIG M BERTHA
12/15/2020 11:21:24 AM