CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214657Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 149177

MEETING REQUEST-
WRITTEN RESPONSES

Sandoz, Inc.
Attention: Gregory Seitz
Executive Director, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Mr. Seitz:[1]

Please refer to your pre-investigational new drug application (PIND) file for Pemetrexed for Injection, 25 mg/mL.

We also refer to your submission dated April 16, 2020, containing a meeting request. The purpose of the requested meeting was to discuss your planned 505(b)(2) New Drug Application (NDA) for Pemetrexed for Injection, based on the approved reference listed drug (RLD) ALIMTA, literature and biowaiver.

Further reference is made to our Meeting Granted letter dated April 21, 2020, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your May 15, 2020 background package.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call me at 301-796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type B
Meeting Category: Pre-IND

Application Number: PIND 149177

Product Name: Pemetrexed for Injection, 25 mg/mL
Indication: Same as indications for the approved reference listed drug (RLD) ALIMTA
Sponsor Name: Sandoz, Inc.
Regulatory Pathway: 505(b)(2) of the Food, Drug, and Cosmetics Act

MEETING PURPOSE

On April 16, 2020, Sandoz, Inc. (Sandoz) submitted a meeting request to discuss their planned 505(b)(2) New Drug Application (NDA) for Pemetrexed for Injection, based on the approved reference listed drug (RLD) ALIMTA, literature and biowaiver.

BACKGROUND

Chemistry, Manufacturing, and Controls (CMC)

Sandoz has developed a liquid formulation of the listed drug (LD) ALIMTA (Eli Lilly), which is a lyophilizate. The LD is available in two presentations, 100 mg and 500 mg per vial. Sandoz is proposing a 25 mg/mL liquid formulation available in three different packaging configurations: 100 mg/4 mL, 500 mg/20 mL, and 1000 mg/40 mL, as a clear colorless to yellow or green-yellow solution for intravenous infusion in each vial.

Nonclinical

Pemetrexed is a folate metabolic inhibitor. Sandoz plans to rely on the LD Alimta for the nonclinical information needed to support an NDA submission for Pemetrexed for Injection. The currently proposed formulation includes propylene glycol and sodium thiosulfate as excipients that are not present in the LD; Sandoz plans to provide a literature-based assessment to support their inclusion at the proposed levels in Pemetrexed for Injection.

Clinical

To support the proposed 505(b)(2) application, Sandoz intends to rely on FDA's prior assessments of safety and efficacy for the LD, ALIMTA. Sandoz does not plan to conduct any clinical studies to support the efficacy or safety of the proposed formulation.

QUESTIONS AND RESPONSES

1) **Is it appropriate to submit the proposed formulation and the additional 1000 mg/40 mL presentation as a New Drug Application (NDA) under Section 505(b)(2) of the Act?**

FDA Response: A 505(b)(2) application appears to be an acceptable approach, based on the information provided. Please also refer to the additional advice below under the heading "505(b)(2) Regulatory Pathway".

2) **Does the Agency agree with the proposal of an additional packaging format of 1000 mg/40 mL for Pemetrexed for Injection?**

FDA Response: FDA has no objection.

3) **Does the Agency agree that no pediatric studies in children 0 to <18 years of age are required?**

FDA Response: Yes. However, Sandoz is still subject to PREA requirements (please see "PREA Requirements" section below).

4) **Does the Agency have any comment with respect to various attributes of Sandoz's proposed liquid formulation?**

FDA Response: The testing attributes listed in Table 1 of Appendix D appear reasonable. In addition, FDA reminds Sandoz that

a) Identification testing is critical for drug product release. Refer to ICH Q6A for a discussion of this quality attribute. The identification test should include either one specific test, or two non-specific tests which are orthogonal to each other. (b) (4) may be appropriate, although other absolute tests may be used.

b) Add a test, method, and acceptance criteria for elemental impurities in accordance with ICH Q3D or provide the results of a risk assessment to support that routine monitoring is not necessary (refer to ICH Q3D).

c) FDA recommends that Sandoz follow ICH Q3A and ICH Q3B and related guidance to establish impurity specifications with appropriate acceptance criteria suitable for the proposed drug substance and drug product.

The adequacy of the drug substance and drug product specifications will be determined during review of the original NDA submission.

5) **Does the Agency agree based on the above information with respect to excipients no additional non-clinical studies are required to support a 505(b)(2) application?**

FDA Response: Based on the assessment of the excipients included in the meeting package, additional nonclinical studies do not appear necessary to support the use of STS or propylene glycol in a 505(b)(2) application. Please include the justification for the safety of these excipients at the proposed levels in the original NDA submission.

6) **Does the Agency agree that no additional non-clinical studies are required to support a 505(b)(2) application?**

FDA Response: FDA agrees that based on the information included in the meeting package, no new nonclinical studies appear warranted to support a 505(b)(2) application for Pemetrexed for Injection. If Sandoz proposes any unique impurity specifications above the thresholds discussed in ICH Q3A/B or higher than those in the listed drug, then Sandoz will need to justify those levels either through a literature-based assessment or a limited duration nonclinical study.

7) **Does the Agency agree that no additional clinical studies are required to support a 505(b)(2) application?**

FDA Response: Yes.

8) **Does the Agency agree that no additional safety analysis of Pemetrexed is needed for the purposes of the NDA submission?**

FDA Response: Yes.

ADDITIONAL FDA COMMENTS

CMC

9) The dosage form *injection* should be used for drug products available as solutions that will be injected, regardless of whether or not they need further dilution before administration. The term *injection* assumes that the drug product is a solution, whereas *for injection* should be used when the drug product is a solid (e.g., lyophilized powder) that must be reconstituted before administration. Refer to the FDA Guidance to Industry, Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format, which is available at https://www.fda.gov/media/110453/download

10) In the NDA submission, include extractable and leachable studies to support the primary container closure system. A complete extractable and leachables study report includes the following information:

   a) Extraction studies on each packaging component using appropriate solvents, including a stronger extracting solvent than the drug product, to obtain qualitative and quantitative extraction profiles. Evaluate the profile of each extract both analytically and toxicologically.

   b) Validation of the analytical methods for extractables/leachables to demonstrate the methods are suitable for their intended use.

   c) Analysis of stability samples for leachables. The original NDA must contain the results of leachable studies that are at least 12 months in duration with the commitment to continue monitoring potential leachables through the proposed expiration dating period.

   d) In addition to container closure, provide leachable/extractable data for all product contact parts of manufacturing equipment, including (b) (4) , etc.

11) FDA reminds Sandoz to conduct primary stability studies with the samples stored in an inverted position. Alternatively, conduct additional stability studies with the samples stored in an upright position.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[4]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when

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[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[5] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application

[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[6]

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[7] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[8]

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[9]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[10]

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[6] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[8] https://www.fda.gov/media/109533/download
[9] http://www.fda.gov/ectd
[10] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).[11] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[12]

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant

[11] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[12] http://www.regulations.gov

may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**

(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(4)	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs,

including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[13]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[14]

[13] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[14] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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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/

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