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Programme and Process of Regulatory Aspects of Drug Master Files and European Drug Master Files

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ABSTRACT

The complexities of the paper documentation required by the FDA to fulfill the needs for even relatively simple submissions mandate the establishment of Drug Master Files with the Bureau of Drugs when feasible to minimize the repetitive submission of routine information. A Drug Master File established with the Bureau of Drugs is a confidential document serving as a reference source for detailed information on a plant facility, plant personnel, chemical process, packaging item or process, manufacture of a raw material and final drug dosage form, equipment, operating procedures, color additives or colorants, clinical studies or animal safety studies, and similar items or processes. The Drug Master File may be utilized either by the “holder” who establishes the file, or by one or more additional parties in support of their application when so authorized by the holder. Typically, a DMF is filed when two or more firms work in partnership on developing or manufacturing a drug product. The Drug Master File filing allows a firm to protect its intellectual property from its partner while complying with regulatory requirements for disclosure of processing details. Drug Master File (DMF) is a document containing complete information on an Active Pharmaceutical Ingredient (API) or finished Drug dosage form. It is known as European Drug Master File (EDMF) or Active Substance Master File (ASMF) and US-Drug Master File (US-DMF) in Europe and United States respectively.

Keywords: FDA, Drug master file, Manufacture, API, European drug master file

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1. Introduction

A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. Drug Master File is a Submission to the FDA of Information usually concerning the confidential, detailed Information

about Chemistry, Manufacturing and Controls (CMC) of a Drug Product or a Component of a Drug Product. The submission of a DMF is not required by law or FDA regulation. A DMF is submitted solely at the discretion of the holder. The information contained in the DMF may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated

New Drug Application (ANDA), another DMF, an Export Application, or amendments and supplements to any of these. As per the regulatory guidelines, it is mandatory to file a drug Master file and after being approved, releasing the drug into the market. A drug master file may be for a bulk drug or for a formulation. A drug Master file declared by the company provides in detail the manufacturing place, physicochemical properties, Pharmacodynamic/kinetic, toxicology studies of the bulk drugs and formulations, therapeutic class, dosage form, strength, route of administration, labeling, packaging etc. Filing a drug master file at USFDA by a company is an indication that the company is claiming its capability in manufacturing and having a facility complying USFDA rules and regulations. Filing drug master files from countries other than United States, give a provision to the US pharmaceutical organizations recommending foreign country facilities utilizing the manufactured products upon approval by the USFDA authorities to market in United States.

A DMF is not a substitute for an IND, NDA, ANDA, or Export Application. It is not approved or disapproved. Technical contents of a DMF are reviewed only in connection with the review of an IND, NDA, ANDA, or an Export Application. Different approaches may be followed, but the applicant is encouraged to discuss significant variations in advance with FDA reviewers to preclude spending time and effort in preparing a submission that FDA may later determine to be unacceptable. Drug Master Files are provided for in 21 CFR 314.420. This guideline is intended to provide DMF holders with procedures acceptable to the agency for preparing and submitting a DMF. The guideline discusses types of DMF's, the information needed in each type, the format of submissions to a DMF, the administrative procedures governing review of DMF's, and the obligations of the DMF holder. DMF's are generally created to allow a party other than the holder of the DMF to reference material without disclosing to that party the contents of the file. When an applicant references its own material, the applicant should reference the information contained in its own IND, NDA, or ANDA directly rather than establishing a new Drug Master file.

2. Methodology

Literature review was done mainly on collection of USFDA and EMEA Legislations and Concentrating on their Drug Master Filing Procedures. The research carried out with the collected data by analyzing the terms of the below parameters:

Types of Study:

The study was conducted with an objective to chalk out the regulatory framework for Drug Master File registration legislations and guidelines. The major emphasis has been provided to regulatory requirements of United States.

Source of data:

Major part of secondary data collection was done by means of following sources

Literature review:

Typically covered the books and regulatory guidelines published officially by Government authorities, including

the academic journals, online journals, market research reports and other resources.

Internet using the web page content:

The literature was collected using numerous search engines e.g. Pharmabiz, DMF search engine, Google Scholar and many more. Online books also served as a good source of information. Key words in the search involved Drug Master File Registration requirements along with the name of various parameters associated to pharmaceutical field, name of regulatory bodies and other variations were used.

Criteria for selection of study parameters:

Part-I: Requirement for Drug Master Filing:

There is no legal or regulatory requirement to file a DMF. Information can be in an Application OR a DMF. A DMF may be filed to provide CMC information that the FDA reviews. The DMF must be submitted in English language. Whenever there is a submission in another language, an accurate certified English translation must also be included. Each page of each copy of the DMF should be dated and consecutively numbered. An updated table of contents should be included with each submission.

Part-II: Documents and study information required for Drug master File preparation. Each DMF submission should contain Transmittal letter, Administrative information about the submission. The DMF will be Reviewed only when it is Referenced in an Application or Another DMF. Holder must submit an LOA (Letter of Authorization-2 copies) to the DMF.

Part-III: Dossier compilation and submission.

All the documents needed for Drug Master File submission should be compiled and should be submitted to USFDA and EMEA in US and Europe Respectively.

3. Results and Discussion

Drug Master Filing in United States

Requirements and challenges to file a DMF:

There is no legal or regulatory requirement to file a DMF. Information can be in an Application OR a DMF. A DMF may be filed to provide CMC information that the FDA reviews. Examples: drug substance, novel excipient. Conversely, there is no need to file a DMF for information that FDA does not Review. DMFs are documents containing proprietary information concerning manufacturing facilities, production details and packaging. In the United States, Canada and elsewhere, DMFs may also cover proprietary support information and excipients. Prior to the initiation, acceptance and adoption of the International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) using their Common Technical Document (CTD) format, each of the major health agencies in the US, Canada, EU, Australia, and Japan had their own formats for the compilation of DMFs. With the adoption of the CTD format, the efforts for preparing a DMF have been simplified. The ICH CTD format has simplified the organization of DMFs for the world's major health agencies. However, there are still many differences in terms of application requirements, number of copies required and CTD Module 1 "Administrative Information and Prescribing Information" formats.

The way the different countries address the paper storage and handling issues brings into play major differences in how DMFs must be prepared to meet each specific country's requirements. For instance, the United States Food and Drug Administration requires two copies of each Type II DMF using the CTD format, but not in CTD module form. Instead, FDA requires one continuous document embracing the CTD formats without the distinction of an "Applicant's Part" or "Restricted Part." This is because FDA considers the entire DMF document confidential and does not have the same marketing application requirements that the EU (European) requires for marketing approval. As a result, one prepares an FDA DMF combining the "Applicant's Parts" and "Restricted Parts" of Modules 2 and 3. FDA also requires one copy in black binders and one in red; and updates must only include the sections changed. The EU requires the entire document to be submitted. However, US marketing applications should be submitted in electronic CTD (eCTD) format. Additionally, FDA agency staffing issues have hindered the update of the DMF guidance document and one should contact the FDA drug master file staff regarding additional and suggested submission information.

Registration Requirements:

Each DMF submission should contain Transmittal letter, Administrative information about the submission. DMF's should contain a commitment by the firm that its facilities will be operated in compliance with applicable environment laws. The DMF must in English language. Whenever there is a submission in another language, an accurate certified English translation must also be included. Each page of each copy of the DMF should be dated and consecutively numbered. An updated table of contents should be included with each submission.

Types of DMF:

In the United States Drug Master Files are submitted to Food and Drug Administration (FDA).

There Are 5 Types of DMF'S in United States.

Type I:

Manufacturing site facilities, operating procedures and personnel not specific to a drug substance are included in Type I. Type I DMFs are no longer accepted by the FDA but old ones remain on file. Type I DMFs are no longer accepted per a Final Rule published January 12, 2000 (65 FR 1776).

Type II: Drug substances, substance intermediates and materials used in their preparation, or a Drug product. A Type II DMF, the most common form, can also cover dosage form drugs manufactured under contract for another company which would file an Abbreviated New Drug Application.

Type III: Packaging materials, from bottles and caps to PVC resin used in their manufacture must be covered in a DMF or other FDA document such as an NDA.

Type IV: Excipients, colorant, flavor, essence or material DMF. Excipients are chemically inactive substances such as starches or cellulose used to bind drug powder together so that it can be pressed into a tablet. Other examples include flavorings in children's drugs, alcohol in liquids, etc.

Type V: FDA accepted reference information not included in the other types.

Submissions to Drug Master Files

Each DMF submission should contain a transmittal letter, administrative information about the submission, and the specific information to be included in the DMF as described in this section. The DMF must be in the English language. Whenever a submission contains information in another language, an accurate certified English translation must also be included. Each page of each copy of the DMF should be dated and consecutively numbered. An updated table of contents should be included with each submission.

General information and suggestions:

Environmental Assessment:

Type II, Type III, and Type IV DMF's should contain a commitment by the firm that its facilities will be operated in compliance with applicable environmental laws.

Stability:

Stability study design, data, interpretation, and other information should be submitted, when applicable, as outlined in the "Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics."

DMF filing process and steps to file a DMF:

Two copies of the Drug Master File with one signed original of the covering letter and other necessary documents are sent to the FDA's Central Drug Evaluation and Research (CDRL). The Drug Master File staff will audit the nontechnical information for completeness and adequacy for submission. If the key elements are missing, the staff will contact the proposed holder to try to obtain the necessary documents in order to file the DMF. Once the DMFs are determined to be acceptable for filing, the document room staffs assigns a DMF number and a letter is sent to the contact person listed in the DMF.

Steps:

- Set the document margins at 3/4 inch for the left (at least) and 1/2 inch for the right.
- Print the transmittal page, administrative information and DMF information on standard letter-size paper. If a larger sheet of paper is required for a diagram or schematic, fold the sheet and attach it to a letter-sized page in a manner that will allow for the page to be opened and refolded. At a maximum, each volume of a DMF should be no more than 2 inches thick.
- Number multiple volumes for one submission according to the total number of volumes (if more than one). (For example, 1 of 3, 2 of 3, etc.)
- Sign all documents requiring signature (only if you are the DMF holder or authorized representative).
- Copy and collate the document; FDA requires you Submit both
- Punch documents with a standard hole-punch.
- Cover each original and copy of each volume with a document jacket. Prepare the submission for shipping and mailing to Drug Master File Staff.

Authorization to Refer To a Drug Master File

The DMF will be Reviewed only when it is Referenced in an Application or Another DMF.

An LOA does two things

- ✓ Grants FDA authorization to review the DMF

- ✓ Grants the Authorized Party the right to incorporate the information in the DMF by Reference.

Holder Must submit an LOA (2 copies) to the DMF. Then send a copy to the Applicant. LOA must contain a specific reference to a particular item in the DMF. This is especially important for large Type III or IV DMFs that contain many products specify the item by its code name, page number and, most importantly, Date of the submission as it appears on the cover letter of that submission (not an internal document date) Volume number not useful When the Authorized Party (AP) changes its name, the DMF holder should issue a new LOA and send a copy to new AP (Authorized Party). It is not necessary to resubmit an LOA on a periodic basis. However: The list of authorized parties should be submitted in the Annual Report.

Withdrawal of Authorization: If a DMF holder withdraws authorization for a customer to reference the DMF this should be submitted as a "Withdrawal of Authorization" document.

Processing and reviewing policies:

Policies Related To Process DMF: Public availability of the information and data in a DMF is determined under 21 CFR Part 20, 21 CFR 314.420(e), and 21 CFR 314.430. An original DMF submission will be examined on receipt to determine whether it meets minimum requirements for format and content. If the submission is administratively acceptable, FDA will acknowledge its receipt and assign it a DMF number. Once accepted, the DMF is entered into the agency database and the holder or its agent should receive an acknowledgement letter. If the submission is administratively incomplete or inadequate, it will be returned to the submitter with a letter of explanation from the Drug Master File Staff, and it will not be assigned a DMF number.

Drug Master File Review:

A DMF is Never Approved or Disapproved. A DMF is reviewed to determine whether it is Adequate to Support the Particular Application that References it. When the Reviewer Receives an Application that References a DMF, the Reviewer goes through the DMF to Determine Whether it requires a Review. The agency will review information in a DMF only when an IND sponsor, an applicant for an NDA, ANDA, or Export Application, or another DMF holder incorporates material in the DMF by reference. The incorporation by reference must be accompanied by a copy of the DMF holder's letter of authorization. If FDA reviewers find deficiencies in the information provided in a DMF, a letter describing the deficiencies is sent to the DMF holder.

Holder Obligations:

Any change or addition, including a change in authorization related to specific customers, should be submitted in duplicate and adequately cross referenced to previous submission(s). The reference should include the date(s), volume(s), section(s), and/or page number(s) affected.

Electronic DMFs

There is no requirement to file DMFs in electronic format. Paper DMFs will continue to be accepted. If this policy changes there will be advance notification. All electronic

submissions must have a pre-assigned number in order to populate in the US Regional. If a DMF available in paper is being converted to electronic format, it is not necessary to request a pre-assigned number.

Companies are encouraged to submit their DMFs in electronic form, including updating current paper DMFs. Note that all applications to CDER, including DMFs that are submitted in electronic format MUST be in ECTD format, unless a waiver is granted. Waivers are not granted for DMFs. All Letters of Authorization for electronic DMFs should specify that the DMF has been submitted in electronic format. A submission in electronic format may NOT be submitted to a paper DMF unless the entire DMF is submitted in electronic format. Companies may convert an existing DMF in paper format to electronic format. The ECTD format provides the backbone for the submission and a guide as to where to place information. It is not necessary to submit all Modules nor is it necessary to submit all sections within a Module. However, Module 1 is required for all eCTD submissions, as it contains the necessary administrative information to identify the DMF. Electronic signatures are accepted for electronic DMFs.

DMFs under GDUFA:

The Generics Drug User Fee Act (GDUFA) section of the "Food and Drug Administration Safety and Innovation Act (S.3187) includes provisions for fees for DMFs, an initial completeness assessment, and communications with DMF holders. GDUFA applies only to Type II DMFs for drug substances (Active Pharmaceutical Ingredients (APIs)) used to support Abbreviated New Drug Applications (ANDAs). It does not apply to any other type of DMF or to Type II DMFs used to support NDA or INDs. The Generic Drug User Fee Amendments of 2012 (GDUFA) is designed to speed access to safe and effective generic drugs to the public and reduce costs to industry. The law requires industry to pay user fees to supplement the costs of reviewing generic drug applications and inspecting facilities. Additional resources will enable the Agency to reduce a current backlog of pending applications, cut the average time required to review generic drug applications for safety, and increase risk-based inspections.

GDUFA is designed to build on the success of the Prescription Drug User Fee Act (PDUFA). Over the past 20 years, PDUFA has ensured a more predictable, consistent, and streamlined premarket program for industry and helped speed access to new, safe and effective prescription drugs for patients. GDUFA will also enhance global supply chain safety by requiring that generic drug facilities and sites around the world self-identify.

Initial Completeness Assessment (CA):

FDA will perform an initial CA once a DMF holder files a Type II API DMF with the generic drug user fee cover sheet (Form FDA 3794) and the fee payment has been verified. The initial CA does not replace the full scientific review, which is performed to determine the adequacy or inadequacy of the information contained in the DMF to support an ANDA review decision.

Information confirmed during initial CA

FDA will use the initial CA Checklist to perform the initial CA. At the top of the cover page of the checklist, FDA will fill in basic information about the DMF, including its name, number, receipt date, and whether the DMF was submitted in electronic or paper format. The FDA will also note whether the primary DMF that is referenced by the ANDA contains any references to other DMFs (subject DMFs). A primary DMF can reference subject DMFs (such as a DMF that describes the manufacture of a material used in producing the active ingredient), which provides additional information needed to completely describe the manufacture of a drug substance.

Before submitting its DMF, the primary DMF holder should check with the holders of any referenced subject DMFs to make sure that they are filed with FDA and are still considered active DMFs. If a referenced DMF is not yet filed or has become inactive, FDA would consider the Primary DMF to be Incomplete. Before assigning a DMF to a reviewer for an initial CA, FDA will confirm that the DMF fee has been paid. If the fee has not been paid, FDA will not assign the DMF to a reviewer for an initial CA. ANDA applicants that reference a DMF for which a fee is due but has not been paid will be notified that the DMF holder has not paid the fee. If the DMF fee is not paid within 20 days after notification, the ANDA referencing the DMF will not be received.

API information included in a generic drug submission:

If a generic drug submission contains all the necessary API information and does not rely on information contained in a DMF, no initial CA will be needed. However, because GDUFA requires collection of a one-time fee for API information included in a generic drug submission, the applicant submitting the generic drug submission containing the API information will be required to pay this fee. Once the DMF fee is received, FDA will evaluate the DMF to make sure it meets the initial CA criteria. If the DMF passes the initial CA, the DMF number will be made publicly available on FDA's Web site. If the DMF fails the initial CA, FDA will send an Incomplete Letter describing the missing elements to the DMF holder.

European Drug Master File:

The European Drug Master File (DMF) procedure may be used when the active substance manufacturer (ASM) is not the applicant for a product marketing authorization (applicant), with a view to protecting valuable know-how on the manufacture of the active substance. European DMFs were established in 1989-1991, revised in 2005 and became Active Substance Drug Master File after Implementation of Common Technical Document in Europe. A DMF is a document containing the information required to demonstrate that the quality of the active substance is adequately controlled by the specification proposed by the applicant. The applicant must, therefore, collaborate with the person submitting a separate DMF to ensure that all relevant information required is supplied. Furthermore it must be ensured that the applicant's part of the DMF contains all information needed for the applicant to take full responsibility for the preparation, including the

suitability of the active substance (as supplied) for the intended route of administration. It is not a requirement to present information on the active substance in the form of a DMF. The information may also form part of the application for authorization to place a medicinal product on the market.

Introduction of API in pharmaceutical industry:

Active pharmaceutical ingredients (APIs) play an important role in the drug product industry. The most obvious contribution is that the API is the active ingredient that makes a drug product effective and provides the pharmacological activity of any drug product or dosage form. The "pharmaceutical industry" at the turn of the 20th century was essentially the local pharmacy (or "chemist" as it was also known). The "bulk pharmaceutical chemical industry" at that time was merely a provider of all those laboratory chemicals, including solvents and excipients as well as APIs needed by the local pharmacist to compound the prescribing doctor's formulation. Over this past century, as with many industries, enormous changes have occurred in the pharmaceutical industry, causing equally significant changes for API suppliers. It is these changes, many of which have accelerated in recent decades that suggested the need for a definitive reference for this manufacturing activity. At one time following routine chemical manufacturing practices would have been sufficient; however, this is no longer the case. Not only has there been a significant shift in the government regulations that control the redefined "quality" of the product, but a very intensive look at the development of the process to be used as well as the manufacturing activities required to make the API. This focus is to ensure that the API is produced in an environment that ensures it is free of contamination that may be introduced from inherent process impurities but also from the manufacturing environment itself. The latter is controlled by the so-called "CGMPs" (current Good Manufacturing Practices), while the former by the nature of the chemical process and the level of quality assurance that the process provides; hence, a focus on the process development is essential. The three overall activities that bring an API to market; the development of the chemical process, the manufacturing activity utilizing that process, and the governmental regulations that control the approval of the product so that it may be commercially marketed.

Contents of drug master file

Applicant's part and ASM restricted part of a European DMF: The DMF contains information which includes valuable know-how which should be kept confidential and submitted to the authorities only. Therefore, it should be divided into 2 parts

- An applicant's part and
- An ASM Restricted Part.

The applicant's part of a DMF is provided by the ASM to the applicant directly and becomes part of the application for marketing authorization. Both the applicant's part and the ASM Restricted Part of the DMF are submitted to the competent authorities. The applicant's part of the DMF is still a confidential document which cannot be submitted to third parties without the written agreement of the ASM.

Applicants part of a DMF:

The applicant must be supplied by the ASM with sufficient information to be able to take responsibility for an evaluation of the suitability of the active substance specification to control the quality of the substance. This normally includes a brief outline of the manufacturing method, information on potential impurities originating from the manufacturing method, from the isolation procedure (natural products) or from degradation and, where applicable, information on the toxicity of specific impurities.

ASM restricted part of DMF:

Detailed information on the individual steps of the manufacturing method such as reaction conditions, temperature, Validation and evaluation data for certain critical steps of the manufacturing method, etc. and on quality control during manufacture may contain valuable know-how. Such information may therefore be supplied to the authorities only. An example is provided in the Table below of the division of the information which should be included in the applicant's part and the ASM Restricted Part, respectively. However, the type of information should always be adapted to the manufacturing method and the characteristics of the individual active substance.

Use of Active Substance Master File Procedure:

An EDMF can only be submitted in support of an MAA (Market Authorization Application) or MAV (Market Authorization Variation). The relationship between the quality of the active substance and its use in the medicinal product needs to be justified in this MAA or MAV. Although the EDMF procedure is developed to keep intellectual property of the ASM confidential, it is also permissible to use the procedure when there is no confidentiality issue between the Applicant/MA holder and the ASM (e.g. when the Applicant/MA holder synthesizes the active substance himself. The EDMF holder may have an EDMF as well as a CEP for a single active substance. Generally, it is however not acceptable that the Applicant/MA holder refers to an EDMF as well as to a CEP for a single active substance of a particular MAA.

Content of MA dossier when active substance master file is USED

The Applicant/MA holder is responsible for ensuring that he has access to all relevant information concerning the current manufacture of the active substance. The specifications used by the Applicant/MA holder to control the correct quality of the active substance should be laid down unambiguously in the MA dossier (NTA (Notice to Applicants)CTD format section 3.2.S.4.1 and 3.2.S.4.2). The Applicant/MA holder should include a copy of the AP in the MA dossier (NTA CTD format section 3.2.S). The version of the AP in the MA dossier should be the most recent and it should be identical to the AP as supplied by the EDMF holder to the Competent Authority/EMEA as part of the EDMF. The Applicant/MA holder should include all relevant details from the AP in the QOS/ER of the MA dossier. In the case of a single supplier and where the EDMF procedure or CEP procedure is used, the specifications of the Applicant/MA holder in the MA dossier should in principle be identical to those of the

EDMF holder or the CEP holder. In cases where the Applicant/MA holder uses a different analytical method than that described in the EDMF, both methods should be validated.

Changes and updates to active substance master file:

A. As for medicinal products, EDMF holders should keep the content of their EDMFs updated with respect to the actual synthesis/manufacturing process.

B. The quality control methods should be kept in line with the current regulatory and scientific requirements.

C. EDMF holders shall not modify the contents of their EDMF (e.g. manufacturing process or specifications) without informing each Applicant/MA holder and each Competent Authority/EMEA.

D. Before implementation, any change to the EDMF should be reported by every MA holder to the relevant Competent Authority/EMEA by means of an appropriate variation procedure.

E. A covering letter should be provided.

F. In cases where the contents of the EDMF cannot be changed for a certain period of time because of other procedural provisions (i.e. mainly because of ongoing MRP procedures), the EDMF holder should still provide the aforementioned data to the MA holder and Competent Authorities/EMEA making reference to this reason and requesting a later date of implementation.

G. The EDMF Holders covering letter to the Competent Authorities/EMEA should contain the following information:

- A tabular list summarizing the changes carried out since the first compilation of the EDMF.
- An overview comparing the old and new content of the EDMF.
- Information as to whether the change has already been accepted, rejected or withdrawn by another Member State.
- The names of the relevant Applicants, MA holders and MAs.
- The new AP and/or RP with each the new version number.
- An updated QOS/ER if relevant.

H. At the occasion of the 5-yearly renewal of a medicinal product, MA holders are required to declare that the quality of the product, in respect of the methods of preparation and control, has been regularly updated by variation procedure to take account of technical and scientific progress, and that the product conforms with current CPMP/CVMP quality guidelines.

4. Conclusion

The Drug Master File is a critical document used to support a drug application. Deficiencies in the Drug Master File can result in the delay of approval of drug applications. It is important that the DMF be filed in a timely manner and that the standards used to compete it are of the same quality as the actual drug application. The DMF can be considered an extension of the drug application. The drug review process works best when the required information flows from the DMFs to the drug application.

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