Regulatory Note

Completeness Assessment of Type II Active Pharmaceutical Ingredient Drug Master Files under Generic Drug User Fee Amendment: Review Metrics and Common Incomplete Items

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Received 14 April 2014; accepted 29 May 2014; published online 18 July 2014

Abstract. Under the Generic Drug User Fee Amendments (GDUFA) of 2012, Type II active pharmaceutical ingredient (API) drug master files (DMFs) must pay a user fee and pass a Completeness Assessment (CA) before they can be referenced in an Abbreviated New Drug Application (ANDA), ANDA amendment, or ANDA prior approval supplement (PAS). During the first year of GDUFA implementation, from October 1, 2012 to September 30, 2013, approximately 1,500 Type II API DMFs received at least one cycle of CA review and more than 1,100 Type II DMFs were deemed complete and published on FDA's "Available for Reference List". The data from CA reviews were analyzed for factors that influenced the CA review process and metrics, as well as the areas of DMF submissions which most frequently led to an incomplete CA status. The metrics analysis revealed that electronic DMFs appear to improve the completeness of submission and shorten both the review and response times. Utilizing the CA checklist to compile and proactively update the DMFs improves the chance for the DMFs to pass the CA in the first cycle. However, given that the majority of DMFs require at least two cycles of CA before being deemed complete, it is recommended that DMF fees are paid 6 months in advance of the ANDA submissions in order to avoid negatively impacting the filing status of the ANDAs.

KEY WORDS: active pharmaceutical ingredient; completeness assessment; drug master file; drug substance; GDUFA.

INTRODUCTION

On July 9, 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) (1) was signed into law (Public Law No. 112–144, 126 Stat. 993, 2012). This law reauthorizes and amends the existing user fee statute for drugs, the Prescription Drug User Fee Act (PDUFA), and establishes two new statutes, the Generic Drug User Fee Amendments (GDUFA) and the Biosimilar User Fee Amendments (BsUFA), which set out fee structures for generic drugs and biosimilars, respectively.

One provision in GDUFA specific to Type II drug master files (DMFs) for active pharmaceutical ingredients (APIs) established a one-time user fee when such a DMF is referenced in an Abbreviated New Drug Application (2) submitted after October 1, 2012. In addition, GDUFA requires Type II API DMFs to undergo an initial completeness assessment (CA) (3) to ensure that the DMF contains sufficient information for a full scientific

review. DMFs that have paid the fee and been found complete in accordance with the criteria set forth for an initial CA are identified on FDA's public website as available for reference (4) in support of a generic drug submission. GDUFA establishes that submissions which make reference to DMFs which are not "Available for Reference" will not be received by the Agency. If the DMF fee has not been paid, the Abbreviated New Drug Application (ANDA) applicant will receive a notification and given 20 calendar days to pay the fee. After 20 days, the ANDA submission will be refuse-to-accept (RTR) and the application fee for the referencing ANDA submission will be forfeited. If the DMF has not passed the initial completeness assessment, the ANDA will be refuse-to-accept and a 75% refund of the ANDA submission fee can be granted.

On October 1, 2012, the U. S. Food and Drug Administration (FDA) launched the GDUFA. The Completeness Assessment of Type II API DMFs was among a few GDUFA initiatives that required full implementation at the start and the draft guidance for industry entitled "Initial Completeness Assessments for Type II API DMFs Under GDUFA" (5) was published on September 28, 2012, to clarify the criteria that FDA will use in the initial completeness assessment. On October 25, 2012, the FDA issued notices in the Federal Register releasing the fiscal year (FY) 2013 fee amounts (6).

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For example, the DMF fee for FY 2013 (October 1, 2012 to September 30, 2013) was set at US\$21,340. This fee very specifically applies only to Type II API DMFs referenced by generic drug submissions (7) under GDUFA (upon the first reference on or after October 1, 2012). This fee should not be confused with the facility fee associated with the API manufacturing facility. It is paid only once during the DMF lifecycle and can be paid independently from an ANDA reference (i.e., no Letter of Authorization to an ANDA applicant is necessary to pay the fee). Once the DMF fee is received and processed by the FDA, the DMF is placed in queue to receive the completeness assessment (8).

COMPLETENESS ASSESSMENT PROCESS OVERVIEW

GDUFA requires Type II API DMFs to undergo an initial CA to ensure that the DMF contains all information required for a full scientific review; therefore, the scope of the review in a “Completeness Assessment” is higher than the administrative criteria used in the Central Document Room for accepting the DMF submission; however, 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 regulatory action, i.e., a “Complete” DMF is not a guarantee it will support an ANDA’s approval, rather it only supports an ANDA’s filing.

The draft CA Guidance establishes two types of CA with different levels of scrutiny that a DMF may receive. A DMF may receive an “administrative CA” review or a “full CA” review depending on the previous review history of the particular DMF. If the DMF has been previously reviewed for chemistry, manufacture, and control (CMC) after November 30, 2007, the DMF will receive the administrative CA review and be considered to have passed the initial CA without further assessment provided that the current DMF status is “active” (9) and the payment status has been verified. If the DMF has not previously been reviewed or the most recent review on record is prior to the November 30, 2007 cutoff date, the DMF will receive a full CA review using the entire CA checklist (10).

Once assigned to a reviewer for full CA, the process follows the general work flow and timeline outlined in Scheme 1. For paper DMFs, the reviewer must request the jackets from the Central Document Room (CDR) and wait 1 to 3 days for delivery before starting the CA review. After the primary review and secondary review are concluded, the finalized review document is checked into the archival system and any incomplete comments are communicated to the DMF holder. A process of notifying the ANDA applicant who references this DMF was implemented in 2013 to promote the active communication between the DMF holder and the ANDA applicant in order to avoid potential refuse-to-accept (RTR) of the referencing ANDA. When the DMF is found incomplete, the ANDA applicant will be notified *via* email of the DMF status (not the actual incomplete comments) and be reminded to follow up with the DMF holder in a few days.

The “Incomplete Comment” letters list deficiencies by the checklist item number along with recommendations on

how to address these items. The DMF holder would address these issues as an amendment to the DMF, clearly identified as a “DMF AMENDMENT FOR GDUFA INCOMPLETE” in the cover letter. Per the instruction in the Incomplete Comment letter, the DMF holder also needs to notify the DMF Review Team by e-mail to DMFOGD@fda.hhs.gov that the amendment to address the incomplete comments has been submitted. This notification will help to avoid any delays in the process with respect to subsequent completeness assessments. Once the DMF is deemed complete, the DMF number, the DMF subject, the DMF holder name, and the date when the DMF was deemed complete are published on FDA’s public website of Available for Reference Type II DMFs for APIs, which is updated on a weekly basis. This list is the mechanism by which the complete status is communicated by the Agency as individual letters are not issued.

As shown in Fig. 1, a very large overall number of DMF payments was received during the first year of the program at a level about 2.5 times the projected number (11). Furthermore, a large bolus of payments was received initially in the first 2 months immediately after the fee schedule was published, creating a challenge to the limited review resources available in the DMF Review Staff (12). In order to efficiently process the high number of CAs received over the first year and reduce the risk to applicant’s having their ANDA’s “Refuse to Receive” due to a DMF that had not passed the CA, a three-tiered prioritization system based on the referencing ANDA priority, referencing ANDA status, and the payment date was adopted during the first year (see Table I) to determine the order of CA assignments for those DMFs needing a “full CA”.

Over the first year, the stratified risk-based prioritization scheme outlined in Table I was extremely effective in reducing the risk to an ANDA applicant of receiving an RTR due to the DMF not passing the CA. Under this scheme, the highest priority is given to DMFs referenced by an expedited ANDA which is in queue for filing review (two common reasons for expedited review are drug shortage and Paragraph IV certifications under GDUFA). These DMFs are at highest risk for causing an RTR because the filing review window is much shorter due to the expedited status, leaving less time for the CA to be completed. A DMF referenced by an ANDA without an expedited status which is in queue for filing review is given the second tier priority due to the longer filing window. DMFs which have not been referenced by a GDUFA submission, thus posing no risk for an RTR, are given the normal priority. Within each priority tier, the DMFs are assigned by the DMF fee payment date with the earliest being assigned first. The status of each DMF in the queue is updated weekly so that newly expedited or newly referenced DMFs can move into the higher priority tiers when appropriate.

By September 30, 2013, the end of the first year under GDUFA, 1,797 DMF user fees had been paid, 1,432 DMFs had received at least one CA review cycle with an additional 137 DMFs assigned but pending CA review. A total of 1,164 DMFs were deemed complete and published on the “Available for Reference List”. The small CA backlog is primarily made up of DMFs with no risk of causing an RTR of a referencing ANDA due to the effectiveness of the

Scheme 1. Process flow for the completeness assessment

prioritization scheme. Of the 184 backlogged CAs in the queue on September 30, 2013, 176 or 96%, were not associated with an ANDA submission; only 8 (4%) were associated with a non-expedited ANDA submission undergoing filing review and none were associated with an expedited ANDA submission undergoing filing review. The three-tiered priority scheme remains in place for all DMFs which pay the fee by December 31, 2013. DMFs which pay the fee after that date are prioritized using a two-tier scheme which retains the top tier for DMFs that are referenced by expedited ANDAs, but which eliminates the middle tier (referenced by non-expedited ANDAs). CA assignment within the two tiers will remain based on payment date. Under the two-tiered scheme, DMF holders and ANDA applicants will take more responsibility for planning a viable submission strategy.

A critical issue impacting the risk of receiving an RTR because of the CA is the timing of the DMF payment and the ANDA submission (13). The time frame between the date of submission of a Type II API DMF and the ANDA submission making reference to it was analyzed for approximately 75 NCE-1 (14) submissions. Only 30% of these DMF payments were submitted more than 60 days prior to the ANDA submission, and 38% were submitted within 30 days of the ANDA submission. Of the 38% submitted 30 days or less prior to ANDA submission, nearly 43% were submitted

within 10 days of the ANDA submission. Clearly, DMF fee payment and ANDA submission timelines such as these do not allow sufficient time for a CA to be completed even under the most favorable circumstances and indicate that ANDA applicants and DMF holders need to plan viable submission strategies under GDUFA.

Another issue observed over the first year of GDUFA was the low rate at which DMFs were complete upon the initial CA cycle. Only about 20% of all DMFs undergoing a CA were found "complete" on the first cycle. Although the requirement for an initial CA for Type II API DMFs is new, the elements of the initial CA have been used previously by the FDA to evaluate DMFs during the full scientific review and the information requirements should not have come as a complete surprise. Hopefully as GDUFA continues, more DMFs will be prepared using the draft CA guidance and first cycle complete rates will gradually improve. Subsequent cycles of CA do decrease the efficiency of the process and increase the risk for an RTR for the ANDA applicant and are a major reason for recommending that a Type II API DMF payment should ideally be submitted at least 6 months in advance of the ANDA (11,13).

The objective of this metrics investigation is to identify the common incomplete items leading to DMF incomplete status, and to provide clarification on how to address these items in order for the DMFs to become complete in subsequent cycles. It is hoped that the information provided from this study will assist industry in preparing high quality DMF submissions so that these issues may be prevented from reoccurring in the future, thus facilitating approval of high quality, safe, and effective generic drugs.

COMPLETENESS ASSESSMENT METRICS (15)

The CA reviews performed during the first 6 months after publication of the DMF fee were selected for this analysis. The first DMF fee payment was received on October 25, 2012, and the last DMF payment date for inclusion in the analysis was April 15, 2013 (16). During this time period, a

Fig. 1. Numbers of paid DMFs by month during GDUFA year 1

Table I. CA Assignment Priority Scheme

Priority (#) ^a	Sorted by	Used for
Expedited (67)	ANDA submission date (earliest first)	DMFs associated with ANDAs in queue for OGD filing review identified as expedited (e.g., Paragraph IV filing or drug shortage).
Referenced (354)	ANDA submission date (earliest first)	DMFs associated with a submitted ANDA in queue for a filing review that is not expedited.
Normal (628)	DMF Fee paid date (earliest first)	DMFs which have paid the fee but are not yet referenced by a GDUFA submission.

ANDA Abbreviated New Drug Application, DMFs drug master files, OGD Office of Generic Drugs, GDUFA Generic Drug User Fee Amendments

^aNumbers of DMFs at a given priority during first 6 months of GDUFA year 1

total 1,049 DMF user fee payments were received. Figure 2 shows the numbers of paid DMFs by month which roughly correspond to the period covered by the study.

These 1,049 DMF user fee payments were received from 300 DMF holders and covered 481 distinct APIs. Approximately half of the DMF holders (144) paid for only one DMF; nearly 40% of the holders (115) paid for between two and five DMFs; about 10% of the DMF holders (41) have more than six paid DMFs each (see Fig. 3).

The majority of DMF payments received over the first 6 months were for paper submissions, with a small percentage of the DMFs in mixed format (i.e., submitted in paper initially and amended electronically later). Less than 20% of the DMFs were submitted in eCTD (or completely converted to eCTD). Figure 4 shows the distribution of submission types.

About half of these DMFs (539 DMFs) had been reviewed for CMC (chemistry, manufacture, and controls) after November 30, 2007, and thus received the administrative CA review. The average time from payment to completion of an administrative CA was just 19 days. The remaining half (510 DMFs), which consisted of DMFs that had never received a scientific review or those where the most recent review was prior to the cutoff date, received the full CA review utilizing the entire checklist. Among the DMFs which need full CA reviews, approximately half of these DMFs had been through the first cycle (243 DMFs) at the end of this 6-month period; the rest were either pending assignment (unassigned, 176 DMFs) or assigned but pending review (uncompleted, 91 DMFs); only 10% of them were deemed complete (50 DMFs) and published on the Available for Reference List after one cycle of CA review (see Fig. 5).

The time to completion of the first cycle CA from the time the payment is made is an important metric for DMF

holders and ANDA applicants who are trying to coordinate the ANDA submission to the CA status of the DMF. Over the first 6 months, the average time from payment to completion of the first cycle for a full CA was about 3 months with 2 months spent in the queue pending assignment to a reviewer. As shown in Fig. 6, queue times doubled for expedited CAs and more than tripled for non-expedited CAs in the January through April time frame. The long queue times were primarily the result of the large bolus of payments received initially in the first 2 months and the limited review resources available since the majority of GDUFA hires had not arrived. As discussed previously, the priority scheme was introduced at the beginning of 2013 in order to reduce the risk to the ANDA applicant for an RTR of an ANDA due to the DMF not being “available for reference”. Though it did not reduce assignment duration for the DMFs with references from expedited ANDAs (the review resource had not been improved much yet at that time and the expedited queue were also backed up), the prioritization scheme allowed the limited resources to concentrate on the “high risk” DMFs with the net effect that “low risk” DMFs had to wait longer in the queue before they could be assigned. As the trend in DMF fee payments decreased after the first 2 months, the initial bolus was cleared, and additional review resources arrived, the “low risk” DMFs with normal priority were cleared gradually with improving queue times.

An additional factor that seemed to have an impact on CA review times and success rates on the first cycle CA review was the DMF submission format. The average review time from the time the assignment was made to the completion of the review cycle was 1 week shorter for electronic DMFs than for paper submissions. This is likely due to the additional time spent on requesting, locating, delivering, and transferring the paper DMFs to the reviewer,

Fig. 2. Numbers of paid DMFs by month during first 6 months of GDUFA **Fig. 3.** Numbers of paid DMFs by companies

Fig. 4. Numbers of paid DMFs by submission types

when compared to an electronic DMF which is available immediately. It was also observed that DMF holders were able to respond 1 week faster on average to the Incomplete Comments for electronic DMFs *versus* their paper DMF counterparts (see Fig. 7). This 2-week reduction in the overall timeline may not seem significant when the queue time was several months; however, it may become critical when the Guidance, ANDA Submissions—Refuse-to-Receive Standards (17), is implemented and GDUFA goal dates become official in the third fiscal year of 2015. By October 1, 2014, the ANDA will be RTR if the referenced Type II API DMF is not on FDA's "Available for Reference List" at the time of submission.

It was also observed close to 40% of electronic DMFs were deemed complete on the first cycle, while only 12% of paper DMFs passed on the initial CA cycle (see Fig. 8). For those DMFs deemed incomplete, electronic DMFs were also identified with fewer incomplete items than the paper ones. One possible reason that electronic submissions fared better than paper submissions is that electronic DMFs were submitted more recently and tend to reflect the DMF holders' awareness of evolving regulatory standards. Another reason could be that the eCTD format provides the backbone for the submission which serves as a guide for what to include and where to place information. Though there is no requirement to file DMFs in electronic format, and paper DMFs will continue to be accepted, electronic DMFs appear to improve the completeness of submission and gain valuable review and response time. The Draft Guidance, Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (18), published in January 2013 highly encourages all DMF holders to submit their DMFs in electronic format (19), including updating current paper DMFs.

Fig. 6. Average assignment and review durations. Asterisk "Expedited" and "Referenced" DMFs are bundled together for this analysis. See Table 1 for priority scheme in detail. *Number sign* the duration was back-calculated for the period when priority scheme was not introduced yet. *Circumflex accent* review duration was calculated for the CA reviews completed during this 6-month period

COMMON INCOMPLETE ITEMS OBSERVED IN COMPLETENESS ASSESSMENT (20,21)

The full CA reviews completed during the first 6 months were analyzed to profile the incomplete items most frequently cited. Figure 9 shows the overall profile of incomplete items which resulted in DMF incomplete status. It is obvious from the profile that some items are more commonly missing or incomplete than others.

The items were categorized and analyzed according to the appropriate CTD section, consistent with the structure of the CA checklist as follows:

- Administrative/General Information (Item #1–12)
- 3.2.S.1 General Information (Item # 13–15)
- 3.2.S.2 Manufacture (Item # 16–36)
- 3.2.S.3 Characterization (Item # 37–40)
- 3.2.S.4 Control of Drug Substance (Item # 41–45)
- 3.2.S.5 Reference Standards or Materials (Item # 46–51)
- 3.2.S.6 Container Closure System (Item # 52–54)
- 3.2.S.7 Stability (Item # 55–58)
- 3.2 R Regional info (Item # 59–62)

The most commonly cited items in incomplete letters from each section are highlighted and discussed in more detail below.

- Administrative Information (Item # 1–12)

Fig. 5. CA metrics chart

Fig. 7. Review and response time impacted by submission types

Item 1, “Subject of the DMF is a single drug substance produced by one manufacturing process”, appears to be fully in compliance in Fig. 9; however, this is only because non-compliance with this item stops the CA review and the DMF holder is immediately contacted to resolve the issue. This is because resolution of this issue usually requires changes to DMF fee payments (i.e., additional payments or refunds) and there have been several instances where DMFs have failed this critical item. A single manufacturing process refers to a single synthetic route with permissible alternatives or minor variations. Some examples of the alternative or variation observed in the submissions include validated reprocess/rework procedures governed by the same control strategy for the routine process, additional micronization leading to different particle sizes of the same API, or minor process variation that is the same chemical transformation with little risk to the impurity profile. Multiple manufacturing sites for a single drug substance in the same DMF would not cause a citation of this item as long as the process utilized at each site is the same.

For the purposes of facility self-identification and payment of fees, GDUFA defines API differently from the way it has been defined historically. The definition of API in GDUFA allows a mixture to be an API “when the substance is unstable or cannot be transported on its own”. In this special case, the DMF for the mixture can pay the fee, undergo a CA, and appear on the Available for Reference List. GDUFA also states that “any combination of an active pharmaceutical ingredient (as defined in the statute) with another component of a drug product for purposes of production of a drug product” is defined as a finished dosage form (FDF). Therefore, a DMF which solely describes the mixing of the API with excipient(s) or the mixture of two or more APIs and that does not qualify as an API under the special case described above is considered an FDF DMF under GDUFA and no fee is due (22).

Fig. 8. Submission quality impacted by submission types

Item 2, “For previously submitted DMFs, the DMF holder needs to submit a complete update”, was cited for more than 10% of the incomplete DMFs. This is the only item for which the answer of “Yes” would result in the DMF incomplete status. Because DMFs with numerous amendments make it difficult to determine the current state of the information in the DMF, the draft guidance on CA (5) establishes that a complete update is needed if it has been more than 5 years or there are more than five amendments to the DMF since the original submission or last complete update. Though the DMF guideline (23) states all changes must be reported as amendments and annual reports are not to be used to report changes in the DMF, it is observed that many annual reports were filed with technical information and process changes. If this occurred, an “annual report” would also be counted in the general guide of five amendments for a complete update. The complete update should reflect the current status of the process and not require reference to any previous submission for information. The requirement for complete update does not apply to the DMF if the entire DMF is in eCTD format because the eCTD format always presents the current state of the DMF. However, if the DMF was originally submitted in paper, and only the later amendments are submitted in eCTD, then the complete update may still be needed. A DMF submission for a complete update should clearly state “Complete Update” in the cover letter for clarity. The subsequent CA cycle will be based solely on the information contained in the complete update.

Item 8, “Contains label with storage conditions and expiry/retest date”, was the most common incomplete item in this section. Some DMFs simply did not submit a copy of the container label; other DMFs missed necessary information on the label, particularly the retest date and storage conditions which are specified in the check list. The storage condition is preferably a numerical temperature range based on the stability studies but using USP terminology associated with a defined temperature limit or range such as “USP Controlled Room Temperature” is also acceptable. Undefined general terms, such as “room temperature” may result in a citation for this item. Having a retest date on the container label is consistent with current compliance recommendations (24). The 21 CFR 201.122 also recommends a caution statement, such as “Caution: for manufacturing, processing, or repacking” and prescription sign “Rx” to be on the label (25).

• 3.2.S.1 General Information (Item # 13–15)

Item 15, “General Properties: Should contain basic information regarding the general properties of the drug substance”, was by far the most common item cited for incomplete DMFs in S.1 section. A list of the common general properties for a drug substance was presented at the recent GPhA/FDA Fall Technical Conference/API Workshop (26). Polymorphism (polymorph, amorphous, solvate, hydrate), solubility characteristics (in aqueous and organic solvents), and hygroscopicity were among the most common missing information.

• 3.2.S.2 Manufacture (Item # 16–36)

Though *Item 23, “Certificate of Analysis (COA) of the starting material from supplier(s)”*, item 24, “COA from the DMF Holder”, and item 27, “Representative COAs for

Fig. 9. Overall profile of incomplete items leading to DMF incomplete status

Reagents/Solvents” have been cited for more than one quarter of the incomplete DMFs they are easily amendable.

Item 17, “If API is synthetic, complete Synthetic Scheme from appropriately supported starting materials. Scheme includes structural representation with reagents, reaction conditions, etc.” is cited for more than one fifth of incomplete DMFs. The requirements for the synthetic scheme were generally met. Occasionally observed missing reaction conditions, reagents or solvents can be easily amended. The emphasis of this item, however, is on the justification of the starting material designation which should be in agreement with the general principles outlined in ICH Q11 (27). This can include, if applicable, manufacturer information (name, address, and contact information, etc.), process information (e.g., flow diagram, description, synthetic route, etc.), discussion on impurities (organic, inorganic, residual solvents, etc.), any spike/purge studies to support the proposed specification for each starting material, and the ability of the analytical methods to ensure the quality of starting materials for their intended purpose. Alternatively, referencing another DMF for such information using an appropriate Letter of Authorization (LOA) is an option. Sometimes, the quality control strategy for the starting material is specific to a given process, the holder may commit to re-evaluate the impact due to changes of manufacturers/suppliers and/or the manufacture process. Notifications of such changes and assessment to the agency and the customer whose applications reference this DMF would be complementary to the quality control strategy.

There were cases where the DMF holders were asked to re-designate the starting material(s) from an earlier point in the manufacturing process, even though much of the information mentioned above was provided. This often occurred when the starting materials did not comply with one or more of the principles outlined in the ICH Q11 guidance. Because re-designation of starting material may require update to many other sections (e.g., synthetic scheme, description, raw material information, intermediate and in-process controls, specifications, stability studies), it typically resulted in a longer response time. If the re-designation of the starting material involves a separate site, the associated facility information should be provided to the referencing ANDA applicant(s) as well for compliance purposes. Amending a DMF with the re-designation of a starting material is quite involved, especially when another site/manufacturer becomes a factor for determining DMF

adequacy. Appropriate selection of the starting material was observed to be a critical factor in achieving “available for reference status” in a timely way.

Item 36, “Contains a summary of Manufacturing Process Development”, is often responded to with “not applicable”, a simple reiteration of the process description, or “completion of validation”. Such DMFs were cited for a lacking meaningful summary of development effort to support commercial process robustness and a sound control strategy. ICH Q11 dedicates section 3 on manufacturing process development and particularly discusses the submission of manufacturing development information. The overall process development summary is the focus of this item. It is helpful that a short summary is provided on how the information gained during development is linked to the control strategy, such as attributes controlled by upstream monitoring, spike/purge studies to support specification limits at various stages, and selection of process parameters and controls. This may include, but is not limited to, citing prior knowledge when appropriate, a discussion on process design, the risk assessment made to determine the probability and severity of a failure mode, strategies to mitigate the identified risks in the process, potential scale-up issues addressed for scale dependent operations, etc. While either a traditional or enhanced approach may be taken during manufacturing process development, the summary should highlight the effort in establishing a commercial manufacturing process capable of consistently producing drug substance of the intended quality.

• 3.2.S.3 Characterization (Item # 37–40)

Item 37, “Basic characterization information appropriate for the material (i.e., NMR, IR, UV, MS, Elemental Analysis etc.)”, were cited for DMFs which did not provide a complete characterization information. As mentioned in the CA guidance, 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. The CA review per item 37 does not evaluate how well the characterization data supports the API structure; rather, it examines the completeness of the characterization data set so that the scientific review can be based on a complete package. The package typically includes, but is not limited to, proton NMR,

carbon NMR, FT-IR, UV, MS, elemental analysis, melting point, specific optical rotation, pXRD, TGA, DSC, DVS, etc. Most of the analyses are one-time tests for characterization purposes, and are therefore not burdensome. A summary of how these data support the structure and physical properties of the API would be helpful. Additionally, discussion of potential impurities, including related substances, degradants, inorganic impurities, residual solvents as well as genotoxic impurities, is needed to satisfy the other items in this section. Tabular forms with structures, names, origins, proposed acceptance criteria and analytical method with LOD/LOQ, etc. would be helpful for ease of review (26).

- 3.2.S.4 Control of Drug Substance (Item # 41–45)

Section S.4 did not generate many citations. Item 43, “Method Validation and/or method verification reports are provided.” is the only one cited in over 10% of incomplete DMFs. This is mostly due to lack of method verification data for the methods adopted from the USP monograph. If a USP method is used with additional control of non-compendial impurities, the method should be validated for these in-house impurities. If in-house methods are used instead of compendial methods, method equivalency data should be provided to demonstrate that the in-house method is equivalent or superior to a compendial method.

- 3.2.S.5 Reference Standards or Materials (Item # 46–51)

On average, Section S.5 has been the most cited section for incomplete DMFs. The four items together, item 48, “For a compendial drug substance, comparative data between the USP RS and the in-house WS is provided for the drug substance”, item 49, “The source, Lot#, CoA for RS and WS are provided for each identified impurity”, item 50, “Physical/chemical characterization data for non-USP reference standards are provided”, and item 51, “For impurities with compendial RS available, comparative data between the USP RS and the in-house WS is provided”, are aimed at examining the reference standard qualification program. Most of the quality control methods are used in comparative modes which require the use of reference standards for quantitation or identification. The quality of reference standards is critical and these materials are highly purified and well-characterized. Reference standards from the USP/NF and other official sources do not require further characterization (28). If a compendial reference standard is used as the primary RS, the lot number and certificate are sufficient. When non-compendial material is used as the primary RS, the material should be of high purity and well-characterized to assure the identity (e.g., by spectroscopic characterization), and the strength/assay (e.g., by mass balance). Working reference standards are cost-effective for routine analysis, and are usually materials qualified against primary reference standards with both identification tests and assays. If the primary reference standard is non-compendial, the Compliance Program Guidance Manual (29) highly recommends establishing the equivalency of in-

house reference standards to current official reference standards when they become available.

- 3.2.S.6 Container Closure System (Item # 52–54)

Similar to items 23, 24 and 27 in section S.2, item 54, “Source, specifications and Representative COA for each material are provided”, is about the material control, particularly the primary contact material and functional secondary packaging components. The specifications typically include description and identification (and critical dimensions, with drawings where appropriate). For non-functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), a brief description is sufficient. Item 53, “Certification statements for contact materials for use in food and drugs are provided” is also referred to as the food safety statement. Reference documentation from each vendor showing compliance for each primary packaging material with 21 CFR (174–186) is the satisfactory response to this item (30). Though these two items were cited for 30 and 10% of incomplete DMFs, respectively, they are also easily corrected.

- 3.2.S.7 Stability (Item # 55–58)

The stability section S.7 was not cited often for being incomplete. As mentioned in the CA guidance, the initial CA does not replace the full scientific review, so does not specify how much stability data needs to be provided in the initial submission of a Type II API DMF. The standard applied for the CA is whether or not an appropriate stability program is in place. Information including the stability protocol, summary, conclusion, proposed retest date, appropriate commitments, and any available data (at least one-time point beyond the initial will suffice for the CA) would demonstrate the existing stability program. It is assumed that the DMF will be amended to include the additional stability data required to meet the standard for scientific review consistent with the Guidance for Industry. ANDAs: Stability Testing of Drug Substances and Products (31). The adequacy of the stability information will be evaluated during the scientific review when the DMF is referenced by a submission.

- 3.2 R Regional info (Item # 59–62)

Item 59, “Firm includes representative Executed Batch Records with translation, where appropriate”, and item 60, “Yields, results of in-process controls, and analytical results for intermediates are provided” were cited together for one third of the incomplete DMFs. Either no batch record or batch records in foreign languages without translation were observed. Submission of a representative executed batch record (EBR) is not only required for type II API DMFs, but also for ANDAs if the drug substance information is included in ANDAs instead of referencing separate DMFs, and ANDAs are also required to submit executed batch records for drug products (32). During the CA, the DMF will be checked for English translations of non-English originals, including, but not limited to, the executed batch record. DMF guidance states that English translations of any documents in the DMF must be accurate, but a separate certification statement that

any translated document is accurate is not required (23). When a DMF holder submits a translated document, it is assumed that the holder is certifying to its accuracy by including it in the submission. An EBR in a foreign language with an accompanying English translation of the master batch record (MBR) would be an alternative if the critical analytical data and operational notes in the EBR are translated into English.

CONCLUSION

The large overall number of DMF fee payments received during the first year of GDUFA was two and a half times the projected number and the large bolus of paid DMFs received in the first 2 months immediately after the fee schedule was published created substantial challenges to the timely execution of Completeness Assessments. The challenge was exacerbated by the limited review resources that were available to perform the CA over the first year. The stratified priority scheme employed for CA assignments worked to effectively concentrate the limited resources on DMFs that were at higher risk of causing a potential RTR for an ANDA submission. As a result, RTRs caused by failure to pass the CA were largely avoided over the first year of the program. Later, as the number of DMF fee payments started to decrease, the initial bolus was cleared, and additional review resources became available through GDUFA hiring, the DMFs with low priority were gradually cleared out of queue with a manageable backlog remaining by the end of the first year. The average review time, especially for non-expedited DMFs, was longer than originally expected, mostly due to the high workload. Although the average review time for CAs is expected to continue decreasing with additional review resources, DMF holders should consider paying the DMF fee as early as possible in order to avoid the potential risk of causing an RTR of the referencing ANDA. When GDUFA goal dates are implemented at the start of fiscal year 2015, the DMFs must be “available for reference” at the time of ANDA submission (allowing for the 20 day grace period), making it imperative that DMF fees are paid with sufficient lead time to allow for the CA. Given that the majority of DMFs require at least two cycles of CA before being deemed complete, and an average response time to the initial Incomplete letter of 45 days, it is strongly recommended that DMF fees are paid at least 6 months in advance of the ANDA submission (11,13). This will require an increased level of communication and coordination between ANDA applicants and their API suppliers in the near future.

DMF holders can positively impact the efficiency of the CA process by improving the quality of their initial DMF submissions. The CA metrics analysis indicates that half of the paid DMFs need a full CA review, but only 20% of those DMFs were deemed complete after one CA cycle. It appears that previously submitted DMFs were not proactively amended or that new DMFs were not prepared using CA checklist as a guide. While it is acknowledged that the CA is a new GDUFA initiative and the CA guidance was not publicly available until just prior to GDUFA implementation, the CA elements have been used previously by FDA to evaluate DMFs during full scientific review and are thus

not completely new. A few recently submitted DMFs included a self-evaluated version of the checklist with remarks in the note sections when the locations of the information are not obvious. Not only did these DMFs pass the initial CA in the first cycle, they also made the CA process efficient for the reviewer. This may be a useful practice for both electronic and paper submissions going forward.

The CA metrics analysis also revealed that electronic DMFs appear to improve the completeness of submission and shorten both the review and response times. In particular, the requirement for a complete update does not apply to the electronic DMF if the entire DMF is in eCTD format because eCTD format can always present the DMF in its current state. This advantage alone can save the holders much effort maintaining DMFs throughout the DMF lifecycle. Though currently there is no requirement to file DMFs in electronic format, and paper DMFs will continue to be accepted, the newly published Guidance, Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, strongly encourages DMF submissions in electronic format.

This analysis of CA reviews performed during the first 6 months of GDUFA identifies the checklist items most often leading to incomplete DMFs. By focusing extra attention on these items when preparing a DMF submission, it is hoped that both the quality of the submissions and first cycle “complete” rate will increase. With increased awareness and familiarity with the procedure and criteria for CAs by DMF holders, it is expected that the CA process will improve in efficiency over the subsequent years of GDUFA.

Disclaimer This article reflects the views of the authors and should not be construed to represent the FDA’s views or policies.

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