Taming the Complexity of Preparing CTD Submission Dossiers

Process optimisation and effective management and organisation strategies are essential components when preparing CTD submission dossiers for drug approval

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"Be prepared." In his book, *Scouting for Boys*, Robert Baden-Powell introduced this motto in 1908 as the basis for successful boy scouting. He defined this as "you are always in a state of readiness in mind and body to do your duty". More than a century later, this succinct advice is more applicable than ever in the increasingly complex world we encounter, in almost any walk of life.

However, despite all the advances in technology and process optimisation theory, medical writers who have prepared documents for submission dossiers needed to apply for approval of a drug can invariably confirm that the experience was, more often than not, quite stressful. Preparing submission dossiers can certainly be complex, and this complexity is compounded when the preparation process is suboptimal and the available technology is used ineffectively. An honest learning of ours, having worked on many submission dossiers, is that, all too often, teams really were not in a state of readiness in mind or body to do their duty, even though, on reflection, the straightforward application of common sense principles should have enabled the team to perform better at all levels.

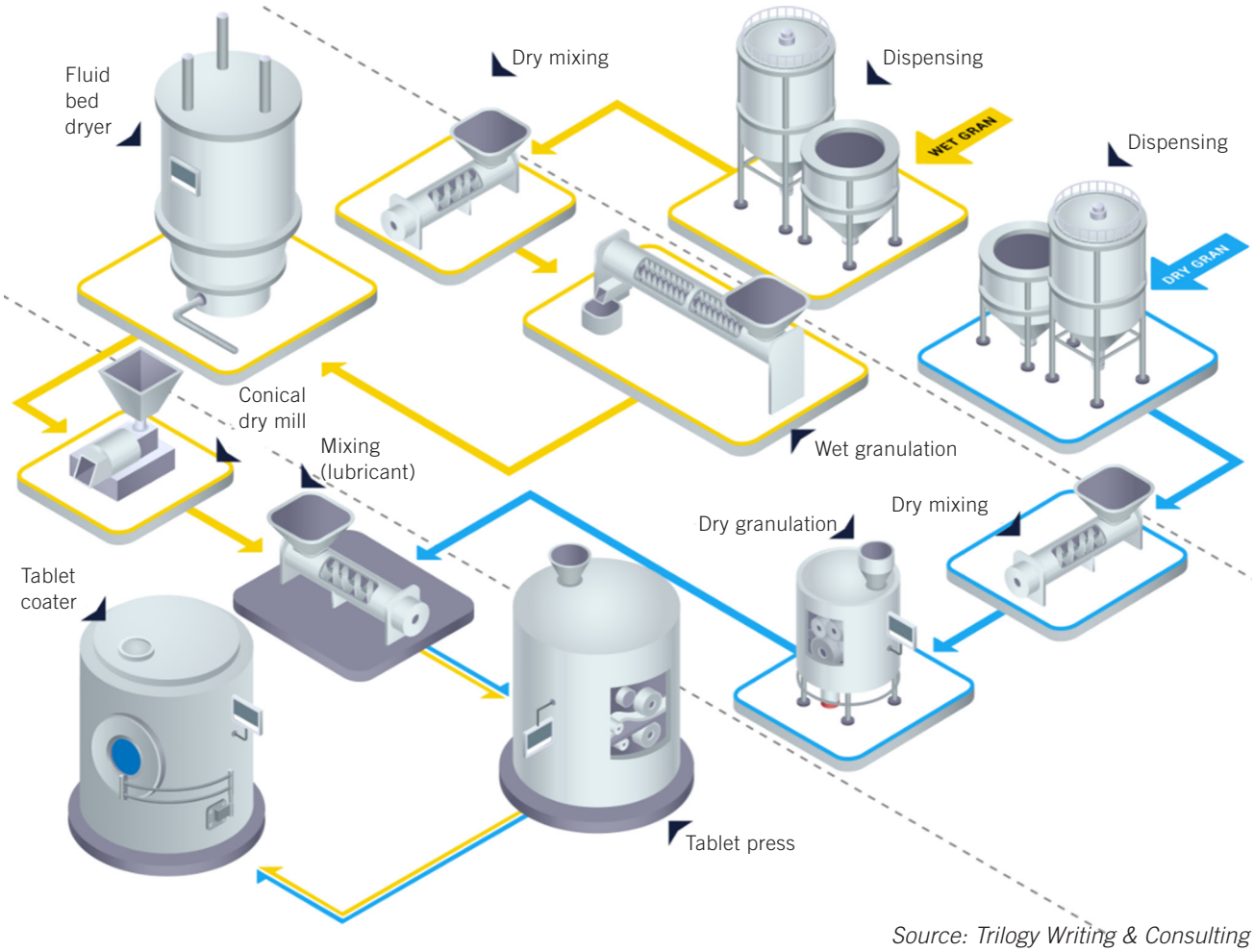
The reasons for this common situation when preparing submission dossiers are myriad. Here, we take a holistic look at some of the challenges encountered by medical writers while preparing submission dossiers and describe solutions that have proven successful at de-stressing the process, thereby increasing efficiency.

Challenges in Preparing Submission Dossiers

Submission dossiers can be highly variable, ranging from multi-indication packages for a new chemical entity to a straightforward supplement or variation for a marketed drug based on a single study. The potential for complexity and the ensuing challenges confronting the medical writer are common to all submissions. To take the extremes, you could have a multi-indication submission prepared with an effective process (and theoretically less stress) or a straightforward supplement prepared with little discernable process (and with much stress).

Relating this to a real-life situation of a submission dossier worked on 20 years ago provides a real-life microcosm of the challenges that can be encountered. With four different indications in a single dossier and no lead medical writer and no central coordination for planning, process, or timelines, the team was a disjointed set of subteams, each with one or more writers working independently of each other on their documents. To compound an already complex situation, the reviewing process was also undefined, involving email distribution of Word files to an often large number of reviewers, even though (20 years ago) the company possessed Documentum™, with the ability to provide a collaborative reviewing tool. There was also a naïve process for resolving and implementing comments that did not work as envisaged. Overall, the project suffered from a lack of management direction and appropriate resourcing to lay out a clear plan and process for preparing the submission dossier.

The result was that, in addition to quality issues with the documents themselves, the timelines for the



Source: Trilogy Writing & Consulting

Figure 1: Typical multi-stage process for manufacturing coated tablets

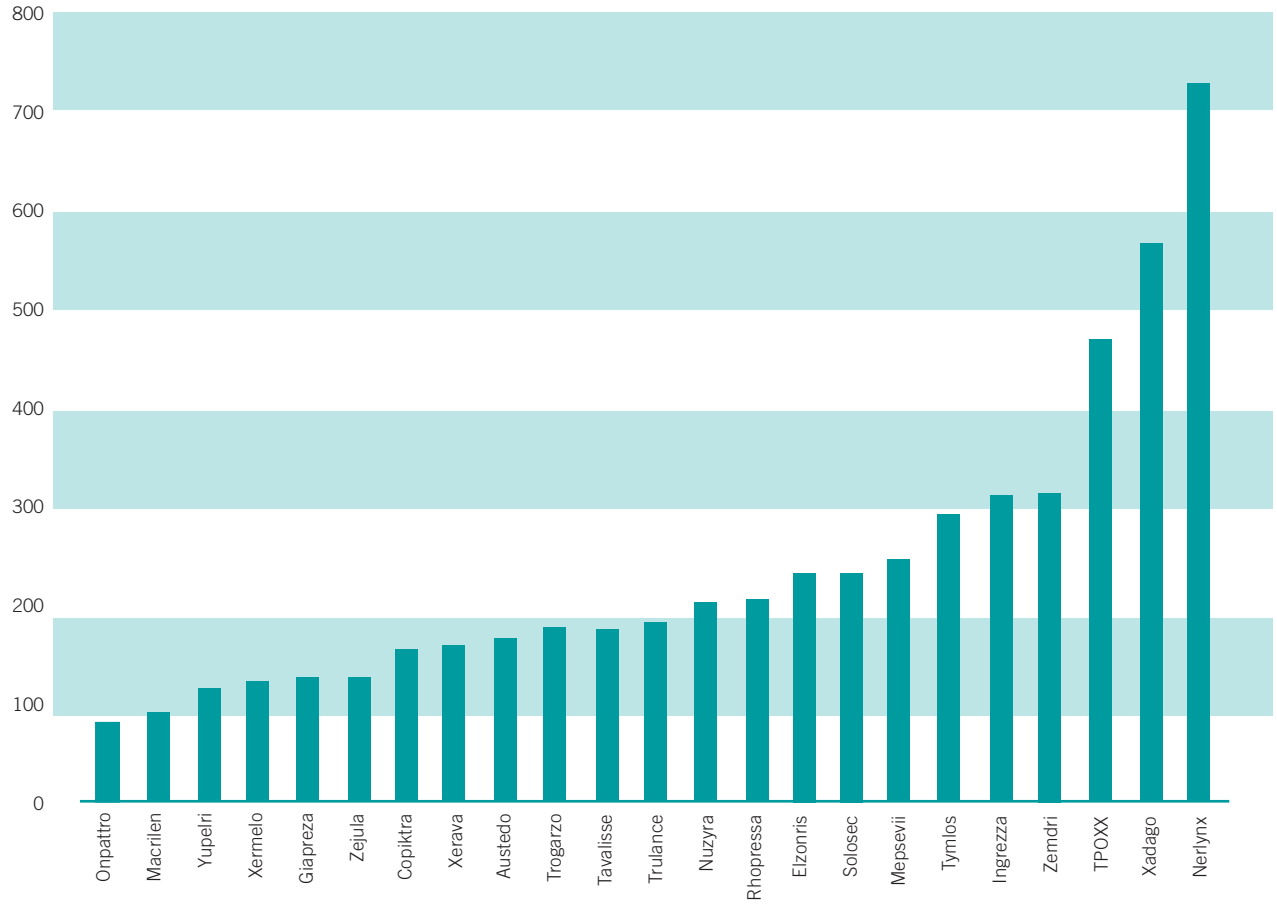
submission were threatened. Now, this was 20 years ago, and the question is justified as to whether such a situation could exist today, given the advances in technology and process optimisation theory for preparing documents, and not least also given increased time and cost pressures. Unfortunately, looking across our spectrum of clients, irrespective of their size, location, or the types of drugs or submissions involved, the answer is clearly yes.

From the medical writing perspective, preparing a submission dossier involves not only communicating the science, but also understanding and applying some important principles of process and logistics. Typically, the medical writer will be more attuned to communicating the science. They may work in a team where others plan and handle the logistics, but this is often not the case, meaning that an awareness of the logistical processes involved and the ability and willingness to invoke them if no one else does can be essential to the overall effectiveness of the medical writer and, in the end, to the success of providing the hard deliverables needed for the submission.

Manufacturing Tablets and Preparing Submission Dossiers

With hindsight, if you're involved in preparing submission dossiers often enough and for long enough, it's easy to view the process (or lack thereof) with a sense of bewilderment. Looking at a different area of the pharma industry, e.g., the steps involved in manufacturing tablets (see **Figure 1**), not only is the process clearly defined, but it's easy to see that the process as a whole has to be meticulously planned and executed, and the component steps feeding into that process themselves must also be meticulously planned and executed; a matrix of plans is needed (subteams) that feed into each other in a coordinated fashion. It is unlikely that anyone would ever question the need for such plans, or ever imagine how the manufacturing process could proceed with anything other than an orderly and rigid process.

So, what does the process for manufacturing tablets have to do with medical writing and preparing submission dossiers? In reality, more than we may care to think. In theory, all the steps required for preparing a submission dossier can be as robustly planned and executed as the process for manufacturing tablets depicted in **Figure 1**. A counter to this idea could be that analysing data and writing



Data compiled by ImprovementatWork

Figure 2: Time (in calendar days) from press release of pivotal topline data to FDA submission for novel drugs approved in 2017 and 2018 (company's first submissions only)

documents is not the same as manufacturing goods such as tablets. However, is this really the case? On closer examination, theoretically, as in tablet manufacture, each step can be meticulously planned, resourced, and executed. Just as a drug substance can be dispensed, mixed with excipients, and granulated in a predefined workflow, so too can data be analysed, a draft document written, reviewed, comments reconciled, etc., in a workflow with a predefined (and realistic) timeframe – enabled by a predefined team according to a predefined process. The process for preparing a submission dossier could be mapped out with exactly the same precision as the process for manufacturing tablets.

While this may sound obvious, in practice, as seasoned medical writers can testify, even if the workflows for each component document of a submission dossier are meticulously planned (which is often not the case), the process can break down for any number of reasons. To take an example, if senior management fails to review a document when required earlier in the process, and then demands substantial revisions later in the process (which may not even be essential to gaining approval, but may nevertheless be demanded when time has not been planned for such revisions), this is no different to senior management requiring a change in tablet formulation after the production line has been planned, installed, and tested. While the latter situation is challenging for logistical reasons, the former situation can occur in some form in almost any submission dossier project. The reason why is quite simply that late changes to a document can be physically implemented even if the time available to do so is insufficient (e.g., writers can work through the night), whereas last-minute changes to a production line are likely to be physically impossible without drastic delays and increases in cost that are highly visible. So, while tablet manufacture can only be viable with meticulous planning and execution (and, therefore, this is the reality), the frequent deficiencies in planning and execution when preparing submission dossiers can usually be ascribed to the fact that the processes involved are more forgiving of these deficiencies.

Stating the Obvious: A Plea for Meticulous Planning and Execution

As time is money, the reluctance of companies to invest resources to meticulously plan and execute the preparation of their submission dossiers is surprising. In essence, the process should be about doing everything possible to optimise the race to market. Based on statistics

gathered from information available in the public domain for novel drugs approved in 2017 and 2018 in the US, a surrogate metric for the time taken for dossier preparation is the time from press release of topline data to submission to the FDA (see **Figure 2**). The median time to submission was 183 calendar days, with a range from under 100 days to over 700 days. We can only speculate on the reasons for such diversity, with scientific, logistic, and financial challenges undoubtedly contributing. However, clearly the aim has to be to minimise the time to submission, especially for a company aiming to market its first product. The financial cost of implementing an effective process to prepare submission dossiers is akin to an insurance policy, and becomes insignificant if a product can be marketed weeks, or months, earlier than would otherwise have been the case.

A useful analogy for the need to minimise the time to submission can be found in the world of motor racing, where the wheels on a racing car have to be changed mid-race within a minimal time by a well-organised team (see **Image 1**). In this scenario, the team has a clear objective, and a clear plan that is drawn up in advance for achieving that objective. Furthermore, the team trains assiduously in advance so that the plan can be carried out seamlessly during the race. Most importantly, the plan is not challenged or amended during the race unless there is no other alternative for achieving the defined objective (i.e., a mistake occurring during execution has to be corrected). In this way, every team member understands exactly what is expected of them and carries out their task exactly when it is required. This is a useful model to apply to the preparation of submission dossiers, and is entirely scalable to their complexity (i.e., multiple documents dependent on multiple sources of information). Preparing a submission dossier is also a race, and exactly as in motor sport, meticulous planning, training, and implementation of the plan during the race is essential for minimising the time to submission.

Image 1: Teamwork involved in changing wheels on a racing car during a Formula 1 race

Five Vital Ingredients for Ensuring Rapid and Effective Preparation of Submission Dossiers

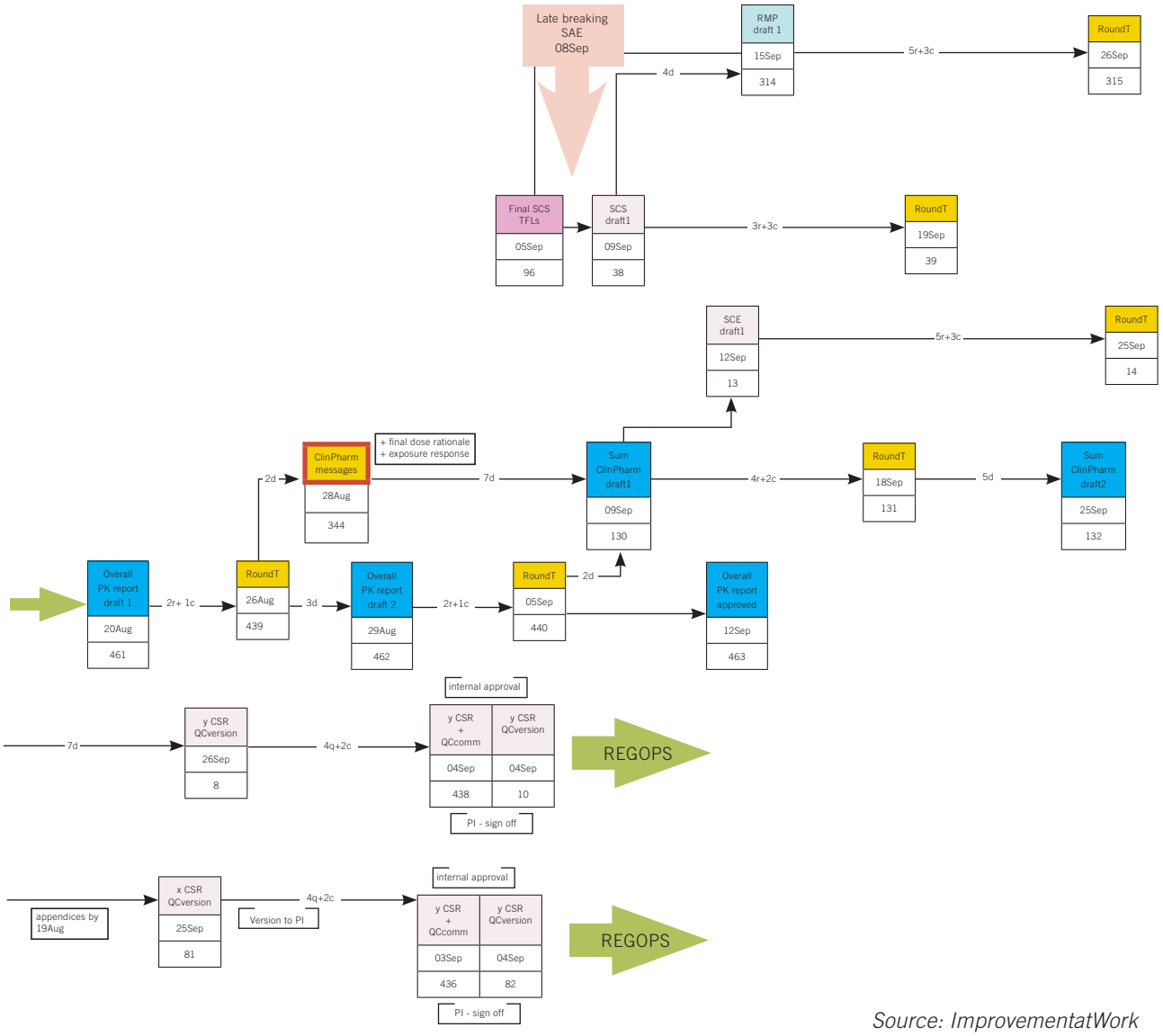
Given the challenges typically encountered, including decision-making pathways, review workflows, and delays in upstream deliverables, there is ample scope for introducing efficiencies into the process applied for preparing submission dossiers. Implemented effectively, a preparation process can yield a generous return on investment. Especially in the situation where a team is preparing a company's first submission dossier, which may be encumbered by the legacy experiences of individual team members, a positive shift in mindset is often achieved by designing and introducing an entirely new process at the onset of the project. In this context, we identify five vital ingredients that are needed for a truly effective process when preparing submission dossiers.

1. Obtain Buy-In From Senior Management

The most fundamental ingredient of all is that senior management (the more senior, the better) recognises the need to implement, and follow through on, a robust and well-resourced process when preparing a submission dossier. If personnel are appointed for this specific purpose, then approving the budget for such dedicated resources at least implies senior management buy-in. For an effective process to be implemented, however, the management buy-in (and associated expectations of the process) must remain visible to the entire submission team at all times to ensure that, across all stakeholders, the focus on the process is not diluted or lost as the project progresses. This is important because a new process can generally only function effectively via top-down enforcement. Depending on the team dynamics, there is otherwise always a risk for the process to degenerate if stakeholders start failing to fulfill their responsibilities, such as providing messaging or reviewing documents on time. If the process starts to unravel, it is generally challenging for the medical writer to enforce the process from the bottom up.

2. Draw up a Detailed Plan Before Preparing the Submission Dossier

Although drawing up a plan may seem an obvious ingredient for any enterprise, the extent of planning for preparing submission dossiers is surprisingly variable across the pharmaceutical industry. Some companies only plan on a macro scale, and planning of the fine details of each step, and associated interdependencies, is often left to chance, resulting in the medical writer



Source: ImprovementatWork

Figure 3: Excerpt from a detailed plan for preparing a submission dossier on a time scale from left to right, indicating inter-relationships between deliverables. Abbreviations: c = consolidation of comments, ClinPharm = clinical pharmacology, CSR = clinical study report, d = day, NCA = non-compartmental analysis, PI = principle investigator, PK = pharmacokinetic, QC = quality control, r = review, REGOPS = regulatory operations, RMP = risk management plan, RoundT = round table comment resolution meeting, SAE = serious adverse event, SCE = summary of clinical efficacy, SCS = summary of clinical safety, Sum ClinPharm = summary of clinical pharmacology studies, TFL = tables, figures, and listings

needing to take the initiative in detailed planning for their own sake.

It goes without saying that, as for the component processes involved in manufacturing tablets shown in **Figure 1 (page 53)**, a detailed plan for how each component document is to be prepared over time, and the associated interdependencies between documents, has to be drawn up in advance. The plan must be developed in collaboration with all stakeholders, i.e., those people who are actually doing the work (not their supervisors), and will typically involve multiple iterations of assessing and challenging the details to derive a robust plan that is realistic for the process and the people involved. To use the analogy in motor sport above, the overall approach should be to prepare everything possible while the car is still on the track (while the pivotal study is still being conducted) before it comes in to have the wheels changed (when the clinical study report and summaries are written). Specifically, such upfront activities should include agreeing on nomenclature, preparing model documents, aligning key messages, preparing patient narratives, etc. In this way, the plan is de-risked as far as possible in advance and stakeholders can focus their attention on critical path activities once the data from the pivotal study are available.

There are numerous options available for documenting detailed plans for preparing submission dossiers, and solutions involving Microsoft Project or Excel are often used. There is no one single tool that is suitable for every type of project or team, but as

visual cues are the dominant means by which humans perceive the world, a visualisation of the plan provides maximum accessibility into the details of the plan. This is no different to an architect's plan when designing a building. For a submission dossier, the type of visualisation that we have used with great success is shown in **Figure 3**. The chart shows the progression of each component over time in terms of dates for draft availabilities, reviewing times, finalisation dates, etc., while at the same time providing visibility of the associated interdependencies between documents. This visibility is especially useful when seeking to mitigate the effects of any delays in upstream deliverables.

3. Nurture the Plan During Preparation of the Submission Dossier

Having drawn up the initial plan in detail, the next step is to recognise that details will change over time, so the plan must be nurtured and issues mitigated throughout preparation of the submission dossier. Typically, as for drawing up the initial plan, this is most effectively done by dedicated resources with the necessary experience because plans maintained by other stakeholders not as their main function are rarely efficient and run the risk of lagging behind events as they occur. Key components of nurturing a plan are regular and structured interactions with stakeholders to confirm that deliverables are on track or, if not on track, to understand why and develop mitigation strategies for any such developments that may threaten timelines.

Among the regular and structured interactions needed with stakeholders while nurturing the plan, we recommend implementing a series of three one-day face-to-face workshops, attended by the entire submission team, to ensure a common understanding of the overall approach taken for the submission, to explain details of the plan, and to define the path forward relative to the workshop in question. Based on the situation of a company's first submission for a novel drug, involving a pivotal study on the critical path, the main components of the workshops are as follows:

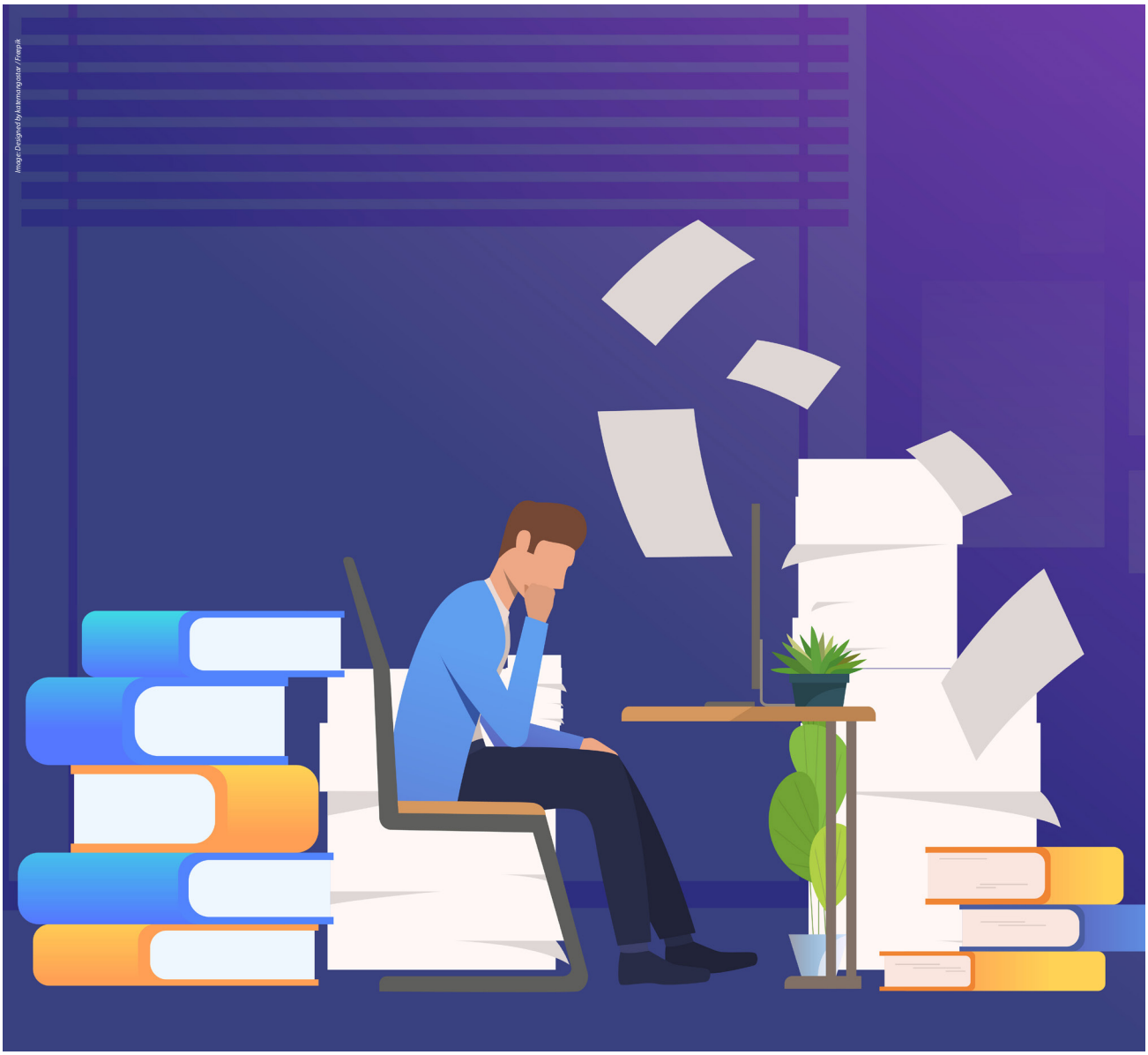
- Workshop 1: Occurs after the initial plan has been constructed, ideally 9-12 months (and a minimum of 6 months) before the planned last patient last visit date of the pivotal study, depending on the submission complexity, to explain the principles of the approach being taken for the submission and to obtain feedback on the feasibility of the initial plan and adjustments needed
- Workshop 2: Occurs 4-6 months before the planned last patient last visit date of the pivotal study. At this stage, based on ongoing feedback, a revised plan is presented to test scenarios for an envisaged submission date and identify critical paths. Attendees work through scenarios to de-risk critical paths and may discuss alternative approaches for all or parts of the submission dossier
- Workshop 3: Occurs 1 month before the planned last patient last visit date of the pivotal study. The attendees test the robustness of the detailed pre-final plan, recommending revisions as needed, so that by the end of the workshop, they are in a position to agree a final plan with an attainable submission date
- After Workshop 3, the final plan should be frozen unless essential adjustments are needed as a result of unforeseen circumstances. This enables the submission team to focus on executing the plan. Returning to the analogy of motor sport, at this stage, the team understands the plan and has prepared accordingly so that all they need to do is execute the plan as flawlessly as possible as soon as the car (data from the pivotal study) comes in to have the wheels changed (when the clinical study report and summaries are written)

4. Provide and Use the Appropriate Tools

Beyond the planning tools described above, there are some specific tools that should be provided to enhance the overall efficiency of preparing submission dossiers. Although obvious, it is vital that the relevant training is also provided to all stakeholders and that the tools are actually used. The training has to not only instruct on use of the tools, but also include explanations of how the tools in question contribute to efficiencies and how using them either incorrectly or not at all degrades not only the process for preparing the submission dossier, but ultimately also reflects a lack of respect for other stakeholders, whose job may be made more difficult as a result.

Three key tools we highlight here for an efficient process are software for collaborative document reviews, a document review matrix to define reviewers, and centralised calendar planning for review workflows.

Software for collaborative document reviews has been available for at least 20 years, but it was only with the availability of more user-friendly and cost-effective cloud-based solutions, such as PleaseReview® or co-authoring in Microsoft Word using SharePoint Online, that this has become what should be an essential tool for any team preparing a submission dossier. The training should include not only instructions on the use of the software itself, but also clear guidance on reviewing expectations, including the need to focus on the reviewer's area of expertise (e.g., a clinician should not spend their time correcting punctuation as this will be checked by a different specialist at the quality control stage), the need to provide actionable comments and revisions (e.g., open questions are not actionable), and the need to review within the defined timeline using only the reviewing tool provided. The efficiencies inherent in using collaborative reviewing software include the ability of reviewers to view and provide feedback on other reviewers' comments during the review, and the automated collation of comments and revisions.



A document review matrix provides clarification of which stakeholders are expected to review each draft of each document prepared for the submission dossier. This matrix, which should be developed with stakeholders early in the project, in parallel to the project plan, can be readily constructed in a Microsoft Excel spreadsheet, listing reviewers by name and function in the first column, and document deliverables by draft in the first row. The role of each reviewer can then be signified in the intersecting cell for each draft of each document by a different colour, depending on whether the individual in question should review only, review and attend the resolution meeting, review and approve, etc. The two main benefits of using a document review matrix are: 1) it ensures that the appropriate stakeholders review the appropriate documents, adding value where it is needed in the writing process, and 2) it ensures that each stakeholder is provided with structured visibility on their obligations for reviewing documents and attending resolution meetings during the entire project, and can plan accordingly. The document review matrix also helps medical writers to ensure that documents are always routed to the correct reviewers.

One persistent issue encountered while preparing submission dossiers is that, with the exception of resolution meetings, the document workflow activities are rarely treated as distinct activities that appear in reviewers' calendars. While project managers cannot be expected to micromanage reviewers' daily activities by the hour or day, they can enforce centralised calendar planning for all review workflow activities. So, in addition to blocking time for resolution meetings, it is helpful to ensure that all reviewers have the review periods for all the documents they are expected to review entered into their calendars as all-day events (not blocking time). As needed, time should also be blocked for triaging review comments and any other workflow-related meetings.

Centralised calendar planning thereby increases the visibility that reviewers and medical writers have of their workflow obligations, and they can then apportion their time accordingly within this framework for reviewing and assessing review comments before triage and resolution meetings.

5. Maintain the Team's Focus on the Plan

An often overlooked factor that can affect the efficiency with which submission dossiers can be prepared is the extent to which stakeholders are enabled to focus on, and prioritise, their obligations within the submission team – in particular, the need to provide information, review documents, and attend meetings as planned. Unless the dossier submission is prioritised at the highest level (i.e., buy-in from senior management has been obtained, see previous), there is a risk that stakeholders may be diverted by other obligations within their company. Analogous to the situation described before for the mid-race wheel change in motor sport, where the team focuses on nothing else but changing the wheels at this critical point of the race, management (and team members themselves) should aspire to reducing or eliminating those potential diversions that stakeholders may otherwise be exposed to during critical phases of preparing a submission dossier. Tasks that can typically be de-prioritised and postponed while preparing the submission dossier include writing manuscripts, conducting routine performance reviews, and attending mandatory trainings and other standing meetings with no direct relevance to the submission in hand.

Conclusions

Despite the fact that preparing a submission dossier needed to apply for approval of a drug (or change the use of an already marketed drug) is a decisive event for any pharma or biotechnology company, our experience has shown that only a minority of companies implement well-planned, focused, and robust processes for preparing their submission dossiers. Instead, many opportunities for leveraging efficiencies are lost, and there is often a risk that the efficiency of preparing submission dossiers is left to chance. This may be an important factor in the substantial variability seen in the times taken for dossier preparation, where the objective should be to minimise this time at all costs.

Much can be learned from considering analogous situations where there is no alternative but to have a well planned and executed process for the task in hand to succeed. With appropriate leadership, organisation, and training of the team, preparation of a submission dossier can be conducted with a similar meticulousness in planning and execution. Regarding precision and speed of execution, to use an analogy in motor sport, the overall approach should be to prepare everything possible while the car is still on the track (while the pivotal study is still being conducted), before it comes in to have the wheels changed (when the clinical study report and summaries are written).

While there are many factors that can influence a team's efficiency, five vital ingredients for a truly effective process when preparing submission dossiers are the need to obtain senior management buy-in to implement, and follow through on, a robust and well-resourced process, draw up a detailed plan in agreement with all stakeholders before preparing the submission dossier, nurture the plan during preparation of the submission dossier to ensure that all the moving parts stay on track, provide and use the appropriate tools for preparing the submission dossier, including appropriate training on all aspects of document workflows, and institute all possible measures to ensure that the submission team can focus on the plan without being distracted by tasks that are not crucial to preparing the submission dossier. These vital ingredients can be applied to the preparation of any submission dossier, irrespective of its complexity, and in practice, our experience has shown that their use has actively de-risked the critical path and contributed to reducing the time needed for dossier preparation.

With a PhD in Environmental Microbiology, **Douglas Fiebig** joined Hoechst (later Aventis) as a Medical Writer in 1996 and has since been involved in preparing the entire spectrum of clinical regulatory documentation. He Co-Founded **Trilogy Writing & Consulting** in 2002 and has prepared regulatory documents for many large and small pharmaceutical companies. Douglas' main focus has been on organising and writing CTD submission summaries, often also providing the medical writing support needed after the dossier has been submitted. He regularly runs workshops for the European Medical Writers Association and other organisations around the world.

As a Chemical Engineer, **Johan Telen** has made a career of improving processes. After 15 years outside of pharma, in 2002, he joined Centocor, a member of the Johnson & Johnson Group as Director Process Excellence and Program Office, and later, in 2005, he joined Tibotec. In 2010, he Co-Founded **ImprovementatWork** to focus on supporting biotech and pharmaceutical companies in the preparation of their first biologics licence application/marketing authorisation application (MAA) and new drug application/MAA. As a submission expert, he works as part of an integrated team with internal regulatory and project management teams, thinking through every detail to ensure organisational readiness for submission.