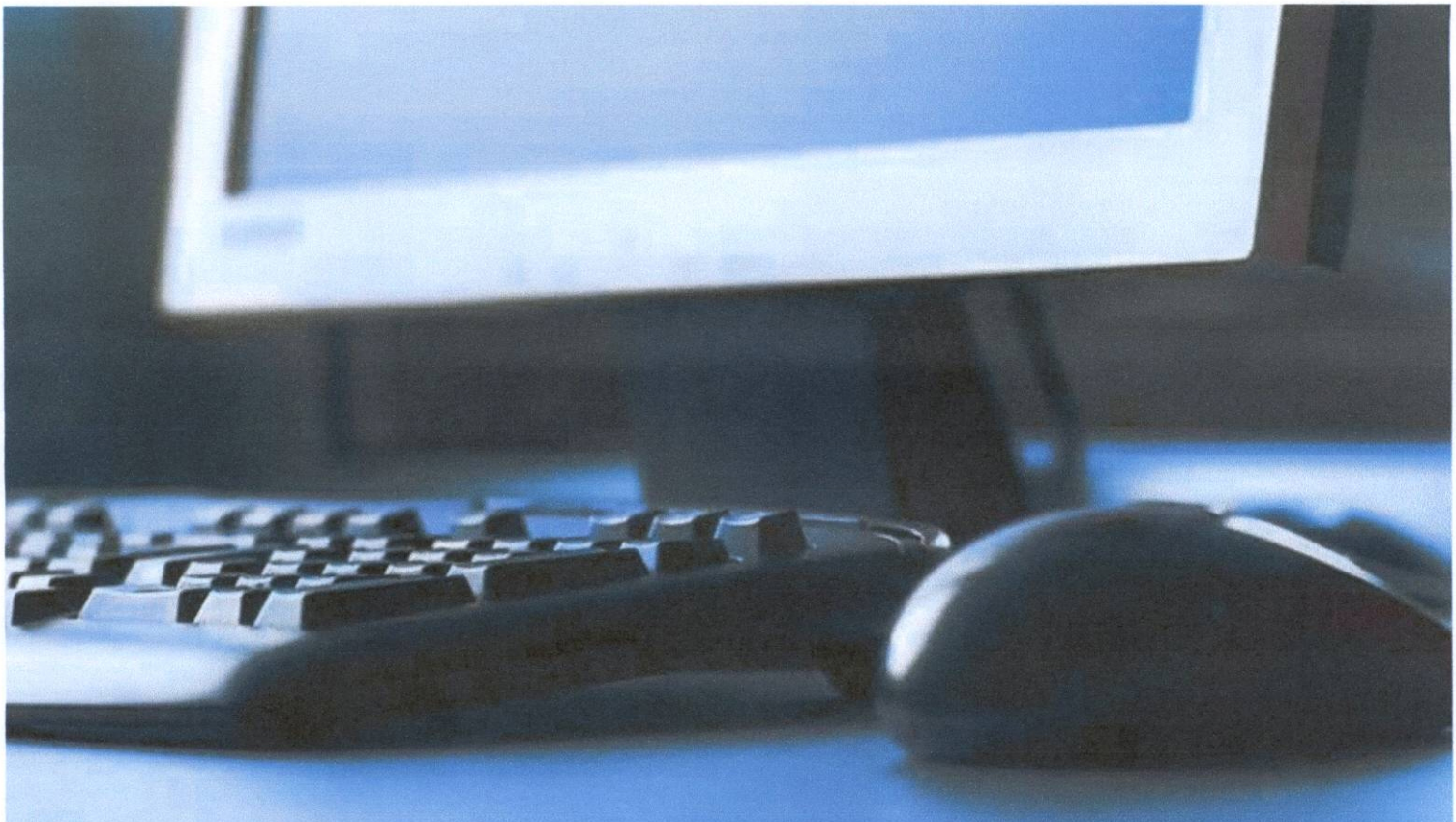


Compliance and the Start-up Company

By Robert Schiff, PhD, RAC, CQA, FRAPS

Start-up companies, whether they are drug, device, biologic, food, supplement or cosmetic organizations, usually have great ideas and concepts for the development, manufacture and marketing of a product. However, they generally have little knowledge of how to comply with regulatory requirements.

At the outset, these companies may have little need to understand the basics of compliance. However, as development proceeds, the start-up should establish a strategy for moving its product through the regulatory maze. The young company may employ a full-time regulatory compliance specialist or can hire outside consultants to guide it in regulatory matters.

What Is Compliance?

The US Food and Drug Administration (FDA), contrary to what many believe, is an enforcement agency. Its responsibility is to determine and ensure that manufacturers comply with federal regulations for production, as well as a variety of other issues.

What is compliance? FDA defines many concepts, even the most elementary. However, I could find no agency definition for compliance. It may exist somewhere on the FDA website, in the voluminous *Federal Register* or the Code of Federal Regulations, but it is not obvious. Wikipedia defines regulatory compliance as "the act of adhering to, and demonstrating adherence to, a standard or regulation." Merriam-Webster goes a little further, citing "the act or process of complying to a desire, demand, proposal, or regimen or to coercion...conformity in fulfilling official requirements."

An interesting part of the latter definition refers to compliance as a response to coercion. Although in the healthcare industry compliance deals with actions in relation to regulations, FDA uses its "guidances" as though they were regulations. Each guidance expressly states that it does not have the force of regulation. Yet if one does not follow the guidance, one needs to explain why. This need to explain is coercive.

What Start-ups Need

Let us consider at what stage the start-up operation first encounters a compliance issue. If a company files a New Drug Application (NDA) using the Common Technical Document (CTD) format,[1] CTD Module 3, section 3.2.P.2 Pharmaceutical Development requires information on development studies to "establish that the dosage form, the formulation, manufacturing process, ...are appropriate for the purpose specified in the application." Other sections require justification of specifications for the drug substance (3.2.S.4.5) and for the drug product (3.2.P.5.6). Therefore, the company should be sure that copious notes documenting the research and development stages are kept to form the basis for the product development report, which is kept at the manufacturing site or corporate offices. This report is available upon request to the FDA inspector during the Preapproval Inspection after filing an NDA or Biologics License Application (BLA). The earlier that the company starts collecting the development information and organizing it, the easier it is to prepare the report.

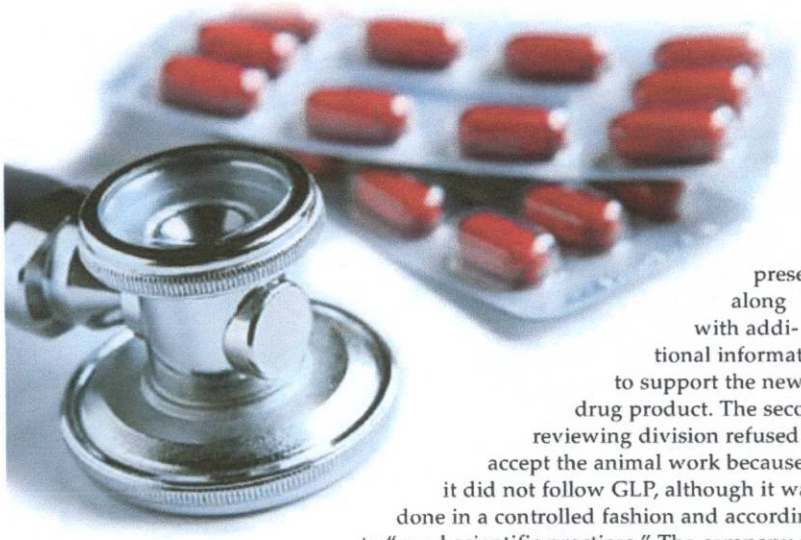
All devices require a design history file[2] and design controls.[3] The latter include the design's development planning, input, output, review, verification, validation, transfer, changes, etc. The Premarket Approval Application (PMA) must include design control information.[4]

In my experience, start-up and early phase companies frequently do not maintain their records in sufficient detail to meet drug and device historical requirements. Just before filing, there is often a rush to gather the information, resulting in omissions or lack of pertinent details. Therefore, the start-up company must establish a resource for information on current regulations, such as a consultant or an employee or board member with the knowledge to help with early regulatory strategy. The company also must maintain complete research and development records to be able to reconstruct the drug or device's development/design history. Compilation of this history by research and development or regulatory affairs personnel serves a dual function: submission and patent filing.

The next point to consider is the preclinical development strategy. To save money, the early phase or start-up company may perform non-Good Laboratory Practice (GLP) animal studies to determine pharmacokinetics, pharmacodynamics, dose ranging and general safety. However, FDA guidance and regulations require animal data (preclinical) to be collected in compliance with GLP.[5] Lacking appropriate regulatory guidance, the company may submit the non-GLP data with an Investigative New Drug Application (IND) in the hope it will suffice to start the trials in man. This lapse may result in a clinical hold or even a rejection of the IND, and additional time and money must be spent to meet the requirements.

The following scenario is an actual FDA prefiling meeting in which I participated. Some details have been omitted because of confidentiality. The company (sponsor) originally presented the active drug substance and drug product for use in an aqueous format, topically applied. Thousands of animals in multiple species were used in trials over a five-year period to support the drug's safety. Most of these were non-GLP studies. Eventually, Phase 1 and Phase 2 studies were approved and Phase 2 is in progress.

The same active pharmaceutical ingredient (API) was presented to a different FDA group for a Phase 1 study. The drug product in the IND contained a different excipient base (available over the counter). Although also for topical use, the drug targeted a different indication than the first example. The same animal data were



presented along with additional information to support the new drug product. The second reviewing division refused to accept the animal work because it did not follow GLP, although it was done in a controlled fashion and according to "good scientific practices." The company pursued a different course; it filed outside the US and is now ready to begin Phase 3 studies.

This story has two conclusions. In the first application, regulatory guidance and strategy should have been obtained before the original animal work was done. In the second, the FDA divisions at the time were neither reviewing consistently nor using the same criteria to judge the animal work. It is FDA practice that when one division has reviewed and approved an IND (and in this case approved a Phase 2 study), the second division should at least consult with the first when the active compound is the same. The second reviewing division refused to follow the practice.

Seek Professional Assistance

A start-up company should listen to its compliance or regulatory advisor. If the advisor notes that a particular course of action may be violative, the company management needs to take a second and even a third look. In addition, an advisor may suggest an action to get an IND approved or even obtain a 510(k) clearance for a device.

As an example, an early phase company was ready to file its IND for a Phase 1 study. It had an active excipient with an API. The latter was furnished by another company and described in a Drug Master File (DMF). The regulatory advisor searched for additional DMFs filed by the API supplier and found some, but not for this type of drug. The advisor suggested that a third party be allowed to view the DMF to determine whether it was compliant. The IND filing company decided to move ahead without third-party review. FDA held up the clinical study for three months because the DMF was incomplete. Granted, it is difficult to review another company's DMF. However, DMF holders may permit review with no copying or removal of the DMF. It should be further noted that the API was supplied from Europe and the US company did not want to spend the money to send someone to review the DMF. The European company granted permission to review the document. This created a serious delay with the clinical investigators.

When a DMF is not complete, the US company does not know FDA's concern or how long it will take to be fixed. As a result, schedules and budgets will have to be adjusted.

The last point I wish to discuss is money. The start-up company usually has limited financial resources. Budgets need to be constructed to finance research and development, compliance and preclinical activities. Too often, the costs of compliance are underestimated and unrealistic and budgeting is performed too late in the development process. Based upon the nature of the drug, its intended use and its delivery, or the type of device, the preclinical activities can be reasonably estimated by a clinical research organization or someone experienced in the field.

Conclusion

The start-up company must keep accurate records of the development of processes and how it arrived at specifications and their values. Tools such as statistical process control (SPC) and process analytical technology can help with the validation of processes and specifications needed for filings. SPC is mentioned here because these tools are very useful in setting specifications. They can be applied to research batches of materials.

Preclinical development and testing must be thought through carefully. The company must determine which portion of the animal testing can be non-GLP and which must be GLP-compliant. Time and financial considerations are paramount in choosing the strategy.

The start-up company should seek compliance and regulatory assistance at the commencement of the project. The advice may save considerable time and money. However, budgets and financial considerations need to be planned carefully.

References

1. *Guidance for Industry: M4Q: The CTD—Quality*. FDA, Center for Drug Evaluation and Research. August 2001.
2. 21 CFR 820.3(e).
3. 21 CFR 820.30.
4. 21 CFR 820.30(j).
5. 21 CFR 58.

Author

Robert Schiff, PhD, RAC, CQA, FRAPS, is founder and CEO of Schiff & Company, Inc., a regulatory affairs, compliance and clinical research organization. Previously, Schiff served in management at a number of companies including the Warner Lambert Company, Hoffmann-LaRoche Inc., J.T. Baker Chemical Company (Richardson-Vicks) Diagnostics Division and Hyland Division Travenol Laboratories (Baxter). He also was an assistant professor in the Department of Anatomy at Tufts University Schools of Medicine and Dental Medicine. Schiff has authored more than 50 publications and holds several patents on medical products. He holds a master's degree from Iowa State University and a PhD from the University of California at Davis. He serves on the boards of several companies, is a member of RAPS Board of Editors, is a Fellow of the Regulatory Affairs Professionals Society and is listed in Marquis' Who's Who in America, Who's Who in the World, Who's Who in the East, Who's Who in Science & Engineering and American Men of Science. Schiff holds the RAC and is a Certified Quality Auditor.