



Lessons Learned and Best Practices in Medical Countermeasure Development

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1.0 INTRODUCTION

If designing and implementing processes that are efficient, successful and adaptable is an art, conforming these processes to rigorous U.S. Government acquisition requirements is a science. While these points may appear deceptively simple, it has taken the combined effort of dozens of dedicated team members—from both government and industry—to arrive at these “a-ha” moments. We offer these lessons and best practices as learning opportunities for even more effective future advances in medical countermeasure development.

2.0 PROGRAM AND CONTRACT MANAGEMENT

2.1 Integrated Product Team Operation and Communication

Lessons: Plan but remain flexible, and communicate in real time.

How often is the phrase “we have a communication problem” heard in business? One of the most comprehensive and important lessons learned is how difficult it is to create and maintain good communication within teams, across teams, throughout the company and with partners and clients; it is something that must be constantly and purposely improved. Remaining flexible is another big lesson. This is not only a necessity in an uncertain scientific research and development environment; flexibility is imperative in uncertain regulatory and government funding environments as well.

2.1.1 Communicate constantly and in real time

A clear communication plan, including subcontractors and client representatives, is essential to any well-functioning integrated product team (IPT). (For an illustration of a sample IPT structure, see Figure 1.) Good communication does not happen naturally; rather, it must be clearly defined and planned, and constantly monitored. Creating a team-specific communication plan should be one of the first action items upon initiation of a new subcontract. This sets expectations for communication, and clearly delineates the appropriate course of action in various situations (for example, reporting a serious adverse event). Team leadership must constantly evaluate communication to ensure that plans are being followed, and adjusted when necessary, to include all stakeholders on the appropriate product communications.

Also—and not surprisingly—bad news doesn’t age well. This may contradict human nature, as the savvy businessperson would generally prefer to present a solution along with a problem. However, clients realize when they are notified of problems immediately that there has not yet been time to develop a solution. Hearing such news in real time provides clients with the opportunity to participate in problem resolution as part of the team.

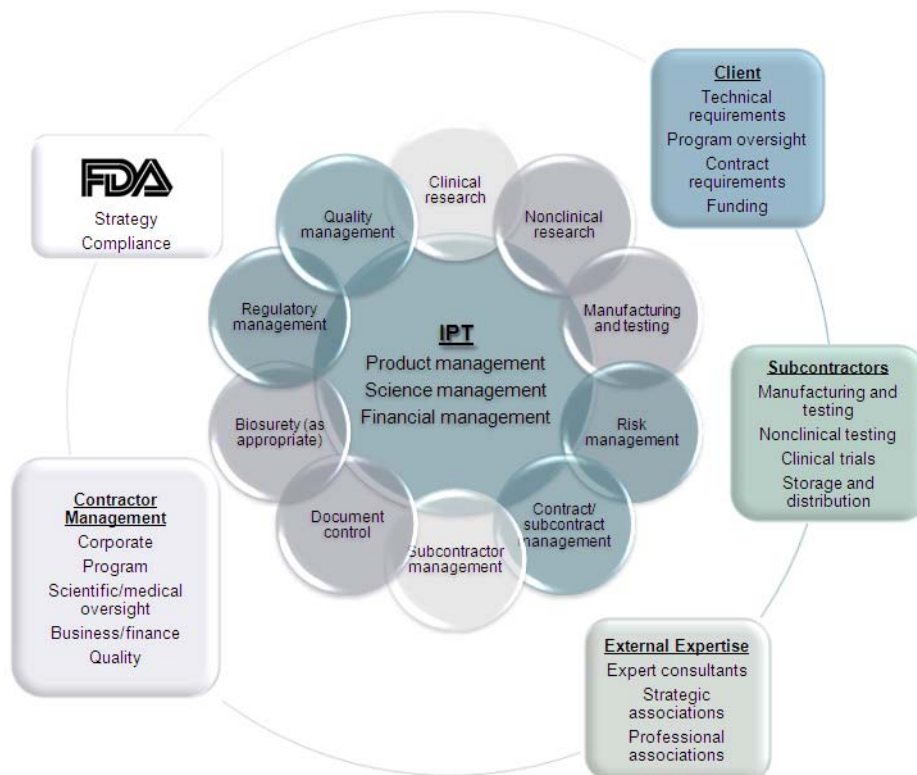


Figure 1 Sample Integrated Product Team (IPT) Structure for a Biopharmaceutical Product Development Program

2.1.2 Plan extensively, but remain flexible

Team leadership must develop and continually refine a detailed product development schedule incorporating not only technical development activities, but programmatic milestones and considerations as well. For example, the product schedule must include key decision points which, in a government contracting environment, are pre-defined by the customer. Technology Readiness Levels (TRLs) for medical countermeasure products including drugs and biologics are used by both the U.S. Department of Defense (DoD) and the U.S. Department of Health and Human Services (HHS).¹

Risk contingency planning is imperative, particularly in a subcontracting environment when portions of development are outsourced, adding flexibility to the process. Mergers and acquisitions are common in the biotechnology and pharmaceutical industries, so the successful contractor must take into account program impact in the event that such a merger were to force closure of a key subcontractor, such as a manufacturer, if these facilities are not available in-

¹ https://www.medicalcountermeasures.gov/Integrated_TRLs.aspx

house. In addition, various regulatory scenarios such as additional required testing should be taken into account and planned for, along with any high-value or high-impact risks.

2.1.3 Understand client requirements, and the reasons behind them

In a government acquisition environment, plans need to be adjusted for cost and schedule: government contractors must distinguish “need-to-know” from “nice-to-know.” This distinction is antithetical to scientists, and therefore the management of most scientifically focused companies. By becoming more customer-focused, contractors will be able to more successfully balance well-defined client requirements with regulatory (scientific) requirements. For example, the Capabilities Development Document (CDD) used by the DoD outlines specific development objectives. Based on such requirements, the contractor should conduct only the necessary scientific studies, and only with advance U.S. Food and Drug Administration (FDA) buy-in where possible (and particularly important for products seeking licensure under the FDA Animal Rule), resulting in a leaner, more efficient—yet scientifically sound—product development program.

2.2 Subcontractor Management

Lessons: Proactively address issues that tend to arise with subcontractors who lack government contracting experience, and nurture relationships with long-term subcontractors.

Writing more comprehensive statements of work (SOWs), and conducting competitions for major pieces of work like manufacturing or clinical trials are two ways to effectively assess costs and improve performance and management of subcontractors.

2.2.1 Develop long-term relationships

Strong and lasting partner relationships are crucial to the ultimate success of product development programs. Considering the multiple years involved in development of any one product, and the millions of dollars at stake if mistakes are made, close professional relationships with subcontractors are the only viable means to achieve ultimate success under the systems integrator approach to medical countermeasure development.²

Key subcontractors must understand the importance of their piece of the product development work, and contractors must not assume that they *will* understand this without a purposeful explanation. When they have a better understanding of the larger program, subcontractors also better understand the implications of delays or failure. Consulting with subcontractors who have the necessary technical expertise before making product decisions helps cement these long-term relationships, ultimately benefiting the program.

2.2.2 Exercise close subcontractor oversight

Sometimes the best choice program-wise may be a company with little or no previous government contracting experience. When advantageous to the program to work with such

² The systems integrator model is discussed further in this publication: House RV, Systems integration: An effective and innovative response to emerging biological threats, Vaccine (2007), doi:10.1016/j.vaccine.2007.01.027.

organizations, the contractor must facilitate the transition into government contracting, helping the subcontractor navigate complex requirements. This ensures that client programs ultimately derive the maximum benefit from these relationships, some of which may become successful long-term business partnerships. Similarly, the contractor may also need to guide subcontractors through the complexities of select agent shipments, both domestically and internationally, to minimize risk to the program cost and schedule.

Having a variety of experts on staff is critical to a contractor's ability to successfully manage complex medical countermeasure development programs; without such expertise in-house, it is difficult, if not impossible, to provide appropriate guidance to subcontractors for the ultimate efficiency of the programs. One mechanism to effectively monitor subcontractor compliance with established protocols and procedures is "person in plant." This contractor employee observes crucial processes at the contract research or manufacturing organization (CRO or CMO) to ensure that subcontractors adhere to exact specifications and, if deviations do occur, communicate changes to the product team immediately. This approach should be standard across all contractor programs. Person in plant not only reduces costly program errors, but also facilitates sharing of knowledge, such as potential manufacturing issues, across programs, allowing for a proactive approach to mitigation.

2.3 Use Appropriate Tools and Methodologies

Lesson: Use the appropriate tools and methodologies to establish a project baseline plan, identify and mitigate risks and accomplish the project objective.

To effectively monitor performance—and understand how the client monitors performance—successful government contractors employ a variety of tools and methodologies to design and implement processes that are efficient, successful and adaptable. These include the earned value management system (EVMS), estimation tools, risk management and market research.

2.3.1 Measure performance with EVMS

EVMS is the primary performance-based tool in the management of DoD programs, and can be used for other customers as well. Contractors must undergo regular audits to obtain and sustain validated EVM contractor status. All program managers should be trained in EVMS, to ensure consistent understanding and application of this tool across programs. Product reports should also be standardized, to better reflect client priorities, including easy-to-find figures such as execution rate.

2.3.2 Employ a combination of estimation tools

To estimate costs, a combination of commercial off-the-shelf (COTS) software, market research and experience is advised. The investment in COTS software facilitates better estimates of the costs of various pieces of work, based on industry averages. For example, software may be employed to more accurately predict the cost of future clinical trials. A key component of success is the ability to estimate costs and anticipate potential risks in advance, so that these can be built into program funding or otherwise mitigated, such as through careful SOW direction.

2.3.3 Maintain a comprehensive risk management program

The successful contractor should implement an overarching risk program to identify, prioritize and mitigate possible program risks before an adverse impact occurs. In a research and development environment, particularly when human clinical trials are involved, this is an arduous task. It is most effective to involve functional area experts to identify potential risks at various stages of development; input from these experts is also crucial to devising effective and innovative mitigation strategies. Risks should be regularly updated and reported to the product teams, with ample opportunity for feedback from all team members, including clients.

2.3.4 Standardize market research to federal acquisition requirements

The successful contractor will also have a formalized process to develop, format, implement and document the market research process, to collect and analyze information about capabilities within the market to satisfy customer needs.

This process should be enacted before completing subcontractor teaming arrangements for all new requests for proposals (RFPs) and/or services valued at \$2,500 or more. This process must adhere to all Federal Acquisition Regulation (FAR) guidelines, and other requirements where applicable, such as the Defense Federal Acquisition Regulation Supplement (DFARS). For example, FAR Part 10 requires agencies to conduct market research for RFPs with an estimated value above \$25,000. By conducting market research for smaller pieces of work, the successful contractor is able to ensure that clients' funds are invested most efficiently and with careful consideration.

3.0 REGULATORY AFFAIRS AND QUALITY

3.1 Experience Licensing a Biodefense Product

Lessons: As early in the development process as practical, begin development and maintenance of an overarching regulatory strategy, and manage the regulatory function in-house.

Contractors must follow numerous regulations, and should also follow many best practices in the areas of regulatory affairs and quality assurance, which are both crucial elements in achieving product licensure. These include early and frequent communication with the agency, developing an overarching regulatory strategy, working closely to help set industry guidelines (such as with the Animal Rule), and taking steps to ensure FDA compliance well into the future (for example, implementing a system for electronic FDA submissions). Quality must also be built into every product development program from the beginning, and the contractor must ensure that subcontractors adhere to the rigorous standards required for FDA licensure during all stages of development.

3.1.1 Begin regulatory strategy development as early as possible

Regulatory strategy development must begin as early in the product process as possible. The contractor should hold early, frequent, detailed and collaborative meetings with the FDA to

obtain crucial buy-in at key points in the product's life cycle. Experience with numerous regulatory strategies is advantageous in developing vaccines for biological and chemical defense, and advancing candidate vaccines and therapeutics through the regulatory pathway to licensure. These strategies include:

- Accelerated Approval
- Fast Track designation
- Orphan Drug program
- Priority Review
- Rolling Submission
- Animal Rule

3.1.2 Manage the regulatory and quality functions in-house

Regulatory and quality functions require in-house management to ensure continuity and success of development strategies. Suggested regulatory practice includes providing detailed technical packages to the agency for comment so that FDA meetings are focused and productive. This approach improves communications with both the agency and clients, and allows easier standardization of best practices across product development programs. (Quality systems are discussed further in Section 3.4.)

3.2 **Animal Rule**

Lessons: Communicate early and often with the FDA, and don't be afraid to help create the rules.

3.2.1 The Animal Rule is not a shortcut to licensure

The FDA's Animal Rule provides a mechanism to demonstrate efficacy of new drugs when human efficacy studies are not ethical or feasible. Few drugs have been approved under this rule, and to date, no vaccines. Use of the Animal Rule will be required for licensure of biological and chemical defense vaccines, requiring a carefully considered scientific strategy, supported by regular and frequent communication with the FDA. To utilize the Animal Rule, relevant animal models must be selected, and bridging studies must be conducted to demonstrate a variety of criteria, including a correlate of protective immunity in humans. Industry groups such as the Alliance for Biosecurity are working to help set precedents in this area.

3.3 **Electronic FDA Submission**

Lesson: Selecting and implementing an appropriate solution for electronic submission of FDA documentation is not easy, fast or inexpensive.

3.3.1 Invest in electronic document management

An Electronic Document Management System (EDMS) is necessary for future regulatory compliance with electronic submissions, and to streamline document reviews and more efficiently maintain version control. Such a system, specifically Electronic Common Technical Document (eCTD) software, once validated and tested, will allow the contractor to electronically

submit documents to the FDA in the agency's preferred electronic format, eCTD. The FDA requires a validated network, which is an ongoing and lengthy process.

Implementing an EDMS and electronic FDA submission capabilities is infinitely more complex than most companies could anticipate—it is not something that could be completed quickly, due to the complexity and FDA validation requirements. Acquiring the system also requires a substantial capital investment (approximately \$500,000), which will be necessary to help ensure the long-term success of client programs.

3.4 Quality Systems

Lesson: Quality must be an integral part of every product development program from the beginning; it must be built into the company's infrastructure, and that of its subcontractors.

3.4.1 Structure the quality organization to ensure neutrality

To ensure regulatory compliance and the highest quality product, the quality function should report directly to the contractor's chief executive or president. This helps ensure that quality management personnel are unbiased in their work, such as interpreting audit findings and determining needed process improvements. A biopharmaceutical contractor's quality system will include Product Quality Assurance (PQA) and Clinical Quality Assurance (CQA), to ensure the production of quality materials and the preservation of human safety, respectively, among other responsibilities.

Throughout the product development process, PQA ensures that material meets the stated specifications, and is in compliance with all applicable regulations and commitments to the FDA as stated in the Investigational New Drug Application (IND). CQA auditors review and approve clinical study documents and procedures in accordance with Good Clinical Practices (GCP), adhering to guidelines and regulations from the FDA, International Conference on Harmonisation (ICH) and Code of Federal Regulations (CFR) as well as all applicable review boards, such as the Data Safety Monitoring Board (DSMB). A robust document control system to manage federally mandated record retention and standard operating procedures (SOPs) is an integral part of the successful contractor's quality systems.

3.4.2 Ensure that quality is part of subcontractor qualification

Quality also plays a key role in subcontractor qualification. Each prospective subcontractor should complete a quality questionnaire, and be audited by quality assurance personnel prior to contract initiation. By personally visiting and inspecting proposed subcontractor sites, potential quality assurance problems can be identified early and prevented before they become major program issues later in development. A quality agreement, annual audits, and frequent communications with quality assurance liaisons are tools that can be used to monitor subcontractor compliance levels.

4.0 OTHER KEY CONSIDERATIONS FOR MEDICAL COUNTERMEASURE DEVELOPMENT

4.1 Technology Transfer

Lessons: Develop good relationships with tech base partners, document all development work, and maximize commercially available components and scalable processing techniques.

A successful technology transfer process is critical to the systems integrator model for product development. Good working relationships and clear, consistent documentation at all stages are vital considerations.

4.1.1 Develop a partnership with reputable nonclinical research facilities

The successful contractor should assess the capabilities of, and establish relationships with reputable, high-quality nonclinical testing facilities through a standard contractual agreement. Pre-qualification of the subcontractor eases contracting for needed work, such as animal studies requiring high biosafety level facilities (that is, BSL-3 and BSL-4). The contractor should also develop an efficient process for obtaining necessary board and committee approval on protocols; these vary based on the client. For example, nonclinical studies conducted on behalf of the DoD require U.S. Army Medical Research and Materiel Command (MRMC) approval of animal protocols in addition to approval from the CRO's Institutional Animal Care and Use Committee (IACUC).

4.1.2 Prepare tech transfer documentation using CGMP format

Process development documentation for tech transfer should be written using either Good Documentation Practices or Current Good Manufacturing Practices (CGMP) batch record format. Although this is not a requirement in early development, and is almost never applied at typical development sites, developing these records prior to beginning work, and including a process flow diagram for easy comparison across experiments provides an advantage in quickly transferring to the new site.

The contractor should require a final report as the last deliverable of all development work. Examples include nonclinical study reports, process development reports, production records, analytical development reports, standard analytical methods, and identification and trending of assay controls. Excellent documentation during technology transfer eases the process and provides added efficiency when developing later documentation, such as regulatory submissions.

4.1.3 Any processing techniques considered should be commercially scalable

To meet client requirements, any processing technique investigated should be commercially available and scalable to the final proposed commercial scale. The resins, filters, chromatography and filtration systems used must be commercially available and typical to commercial manufacturing, to ensure both supply and cost effectiveness. The contractor must work with CMOs to ensure that they understand the value in meeting manufacturing requirements as part of critically evaluating a process received from a development laboratory and translating it into a commercially viable process.

4.2 Novel Regulations

Lesson: Work closely with the responsible parties and those affected by the changes when implementing new guidance.

4.2.1 Use an IPT approach to standardize response to novel regulations

The successful contractor must actively work with the client to address novel or changing requirements. For example, when working on behalf of the DoD, biological select agents and toxins (BSAT) regulations include implementing physical security requirements and the Biological Personnel Reliability Program (BPRP). Each set of regulations has unique requirements that must be addressed in conjunction with all parties involved including the contractor, subcontractors, client representatives and, in some cases, representatives from the governing body. In fact, asking the governing body for guidance may be a necessity in the case of newly implemented regulations, where industry expertise may be sparse or nonexistent. An IPT approach works well to manage compliance with various such requirements, and ensures program continuity to the extent possible by involving affected subcontractors and other stakeholders.

4.3 Clinical Trial Management

Lesson: Different expertise is required early in medical countermeasure clinical research and development than later in advanced development, particularly to successfully design and manage human clinical trials.

4.3.1 In-house clinical expertise is critical in late-stage development

Clinical trial design and management is not one-size-fits-all. An experienced clinical team with vaccine trial design and management experience (including clinical data management systems), is a crucial component of achieving successful FDA licensure. In addition, experience with later-stage trials, including Phase 3 trials and post-licensure requirements, will be essential to developing licensed medical countermeasures. A larger and more experienced clinical staff is crucial, particularly in the management of large multi-center studies, due to the inherent complexity of such research, and to manage the infinite variability inevitably inherent in researching human subjects.

4.4 Nonclinical Research and Testing

Lesson: Build animal models and assays carefully from the beginning, with the end objectives in sight.

Careful selection and development of animal models and assays to assess the immune responses are critically important, especially for product development under the Animal Rule. To bridge the animal and human data, well-characterized challenge material and reagents will be needed to develop acceptable animal models and validated assays. The vaccination and challenge animal models may also need refining during product development to more closely reflect the human immune responses to the vaccine, which is needed to bridge efficacy in animals to predicted clinical benefit and effective dose selection in humans—a must to support licensure.

5.0 SUMMARY

Managing biopharmaceutical development programs will never be a simple endeavor. To ensure success—at least to the extent possible in a research and development environment—several best practices are recommended in the areas of program and contract management, regulatory affairs and quality, and planning for future requirements.

When developing medical countermeasures, it must be done right the first time. There is no room (and no budget) for error. Good communication and *systems* to ensure the flow of communication are a must. Understanding client requirements and the *reasons* behind them is critical, as is using appropriate tools and methodologies to establish a project baseline plan and identify and mitigate risks. Excellent subcontractor management practices are also essential, including developing long-term relationships and closely overseeing subcontractor work.

Perhaps to best understand and prepare for the future of medical countermeasures, we must consider past lessons learned, building on the combined experience of both government and industry to better protect against both naturally occurring and man-made biological threats. It is with this goal in mind that these lessons learned and best practices are offered, not as a comprehensive guide, but a glimpse into the myriad complexities of developing medical countermeasures on behalf of government agencies.