

Keys to success in developing medical countermeasures for the Department of Defense

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The absolute essentials

- Understand the customer
- Understand the requirements
- Understand the risks

Working for the DoD: It's like working for the government, only more so

- There are a multitude of regulations (FAR, DFAR, etc.)
 - Nontrivial to get into the business
 - Nontrivial to remain in compliance
 - Limited flexibility and agility to respond to changing circumstances
- **Understanding acquisitions processes is essential.**
- The contracting vehicle must be seriously considered prior to inking the deal. All have pros and cons.
- Budget and schedule are driven by different considerations than in the commercial world. Ignore those differences at your peril.
 - Nothing turns on a dime.
 - Nothing costs “just a little more”.
 - Everything carries second- and third-order consequences. Learn to see over the horizon.

Build the team

- Make the customer part of the team.
 - The Integrated Product Team concept works
 - Think in terms of partnership, not provider
- As with any human interaction, communications can and will break down, so structure a communications plan accordingly.
- Assume that expectations are never going to be clear enough to either party.
- Place high priority on ensuring complete and bidirectional transparency.
- Over-communication is sometimes as bad as under-communication.
- “Bad news does not age well”.
- Successes are to be shared, internally and externally.

Never assume...anything

- Never assume you know the customer's needs better than they do.
- Never assume you fully understand the customer's needs. Constant triangulation and verification are essential.
- Never assume success. Plan for failure.

What are you building?

- The most important criterion: build with the end in sight
- Product developers need requirements that are clear:
 - What is an acceptable level of protection?
 - How quick should it work? How long should it last?
 - What is the final indication?
 - What is the final format expected to be? (Single-dose, multi-dose, filled syringes, something else?)
 - What is a “licensable” product?
- Product plan must not radically change over time:
 - Product development plans must be flexible, but cannot be anarchistic.
 - Animal Rule provides many daunting challenges, and approach to compliance should be set early.

It all starts with the requirements...

- We need to know:
 - Nature and identity of threat
 - Level of protection required
 - Onset vs duration of protection
 - Administration strategy
 - Storage conditions
 - Initial delivery amount
 - Ongoing requirements
 - Regulatory strategy
- Because:
 - Specificity of the response
 - Preclinical and clinical study design
 - Administration and testing paradigm
 - Clinical strategy
 - Formulation, stability and format
 - Manufacturing strategy
 - Manufacturing strategy
 - Overall program design (licensed vs. unlicensed)

Deviations from the plan always result in significant cost and schedule ramifications. A clear plan for development of the product is necessary in advance, and modifications should be made only when absolutely necessary.

Understand need-to-know v. nice-to-know

- **Hard, cold fact:** there is not an unlimited pot of money, even for Uncle Sam. Therefore, needs must be prioritized.
 - Funding cycles are anticipatory of work, and fairly inflexible
 - Little chance to ever “catch up” in funding if you blow the budget
- Product development life-cycles must be designed to reach the goal (FDA licensure in most cases) as efficiently as possible while balancing risk considerations.
- Budgets are intolerant of pure-science endeavors that do not directly contribute to achieving the objective.
- This is not an academic exercise!



Risk aversion: It's all relative

- Identify all conceivable risks and their interconnections and dependencies
- Assess likelihood and impact
- Establish risk severity index
- Determine potential mitigation(s)
- Establish contingency plans
- Review and re-evaluate constantly
- Maintain recovery planning
- Communicate risk to stakeholders

Probability of occurrence

X

Impact on:

Performance

Schedule

Cost

= Risk Severity Index

**Risk Severity Index guides
resource allocation to retire
risks early and often.**

Risk management is crucial to success

- Murphy's Law is first, last and always the operating principle in developing medical countermeasures
- Development of biodefense medical countermeasures is inherently a high-risk enterprise:
 - Lack of prior art (make it up as you go).
 - Compliance with the Animal Rule still a wild card.
 - Will things work when the time comes? (Hint: they must.)
 - Logistics of use still being worked out.

Uncertainties increase the risk

- How much product will be required?
- How will it be stored?
 - Improvement of products with exotic adjuvants may add substantially to formulation time.
 - Novel methods for enhancing storage will affect overall production timeline and difficulty.
- In what form will the countermeasure be supplied?
- What is the anticipated storage life of the product?
 - Goes to the issue of turnover and sustainability.
- How adaptable will current manufacturing technology be to rapidly evolving technology?
 - Protracted nature of biopharmaceutical manufacturing as it is currently practiced is antithetical to quick response and change in processes.
 - This effect is multiplied by government contracting practices.

Risk assessment and management

- Products may fail at any stage during development:
 - Multiple solutions developed with logical down-select.
 - Development of complementary countermeasures and approaches.
- Subsystem management:
 - Careful selection of subcontractors and strategic partners at the outset, and maintenance of the relationships.
 - Creation of incentives and disincentives.
 - Develop redundancy in all key systems (nonclinical, clinical, manufacturing) and all suppliers (when practical).
 - Robust technology transfer capability to facilitate quick turnaround of facilities.
 - Consortium development and management.

Long-range risks in countermeasure development

- Loss of crucial resources:
 - Crucial subsystems may go out of business.
 - Crucial subsystems may experience a change of business focus or business model.
 - Mergers and acquisitions
 - Loss of confidence (technical/regulatory).
- Losing access to technology:
 - Intellectual property restrictions.
 - Technology failure.
- Technical setbacks and unintended consequences.

Conclusions

- Working with the DoD entails differences from either civilian government or commercial customers. Understand the landscape (regulations, culture, processes, etc.)
- Foster a partnership early, and nurture the relationship.
- Never assume anything.
- Never fear to ask the stupid question.
- Understand, anticipate, and mitigate risks.