Measuring the Success of the UTMB-FDA Course: Achieving Data Quality and Integrity in Maximum Containment Laboratories

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Learning Objectives

1. Identify the regulatory expectations of executing Animal Rule studies in maximum biocontainment laboratories
2. Describe conditions that may impact the quality and integrity of the data
3. Outline the course impact on the Medical Countermeasure (MCM) community

Background

Medical countermeasures (MCM) are developed to prevent and/or treat infections against microbial agents that threaten human health. To facilitate MCM development, the United States Department of Health and Human Services Food and Drug Administration (FDA) published the final rule for *New Drug and Biological Drug Products; Evidence needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible* (21 CFR Parts 314 and 601, **Federal Register**, May 31, 2002). The rule, which allows the equivalent of human phase III clinical trials to be performed in animal studies when human studies are not ethical or feasible, is often cited as the "Animal Rule."

The Animal Rule recommends compliance with the Good Laboratory Practice (GLP) regulations (21 CFR Part 58) to the extent practical. Because of the high risk, lethality and potentially highly infectious nature of the disease-causing agents that fall under the purview of the Animal Rule, these studies are often performed in high or maximum (BSL3/4) biocontainment laboratories. The logistics of assuring accurate and reliable data are collected and transferred from BSL3/4 laboratories, conducting the study under regulatory oversight and meeting FDA expectations for characterizing the animal disease model(s) are challenging and complicated. Only four products were approved in the ten year period following publication of the Animal Rule.

Methods

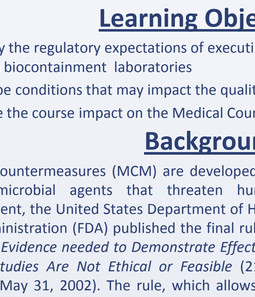
In order to gain a better understanding of the complexities involved in executing these studies, the FDA and the University of Texas Medical Branch at Galveston collaborated in 2012 to design and implement a **training program** to cross educate sponsors, scientists, veterinarians, physicians, nurses, quality assurance personnel, regulators, reviewers, and policy-makers to enable the conduct of regulated studies and associated product approval via the Animal Rule pathway. The training program included a five day face-to-face course in addition to an on-line education module covering the GLP regulations and the roles and responsibilities of Institutional Animal Care and Use Committees. An interactive mock BSL-4 laboratory was included as part of the course.

Course Structure

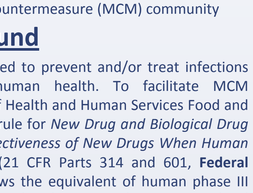
Online Education

Prerequisite Knowledge: GLP, IACUC

11 CEUs



On-line Syllabus



Example slides from on-line modules

Face-to-Face (F2F) Course Daily Overview

29.5CEUs

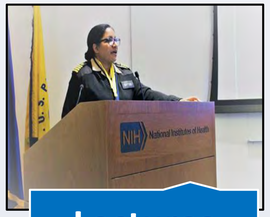
Day 1	Day 2	Day 3	Day 4	Day 5
Reviewing the Infrastructure and Developing an Animal Model of the Human Disease for Use in Efficacy Studies Conducted in BSL-4	Working in a BSL-4 Environment (BSL-4 Mock-Lab Training)	Animals as Substitutes for Phase 3 Subjects, Agent Characterization, and Electronic Data Considerations	Working in the BSL-4 Environment (Site visit to a working BSL-4 laboratory)	Putting the Regulatory Pieces Together

Results

The face-to-face course offered a unique opportunity for members of the regulatory and scientific communities to solve complex issues in an interactive educational environment. Each year, the course reached capacity and a subsequent waiting list for the next year's course is initiated a year in advance. Evaluation results have been consistently positive and participants have indicated that they will apply knowledge learned during the course and the newfound knowledge will result in the improvement of patient/public health outcomes. In 2016, 96% of respondents indicated they would like to attend the course again in the future; repeat course attendance has been documented. From 2013 to 2016, eight additional products have been approved through the Animal Rule pathway.

Topics

- Animal Rule regulations
- GLP regulations
- Good documentation practices
- IACUC protocols
- Veterinary pathology
- Telemetry
- Supportive care and euthanasia
- Surrogate endpoints
- Disease agent characterization
- Assay validation
- Clinical application of Animal Rule studies
- BSL-2/3/4 comparison
- BSL-4 equipment
- Testing facility management
- Role of the Study Director and Quality Assurance



Lectures

Simulations

Mock BSL-4

Target Audience

- Sponsors
- Scientists
- Veterinarians
- Quality assurance
- Nurses
- Physicians
- Project Officers
- Regulators
- Reviewers
- Policy-makers

Attendance by Category (Faculty and Attendees)

Course Date	Location	International	Business & Industry	Academia	Government (%FDA)
April 24-28, 2017	NIH/Ft. Detrick	7.92%	11.88%	15.84%	64.36% (20.79%)
April 25-29, 2016	NIH/Ft. Detrick	9.18%	7.14%	20.41%	63.27% (23.47%)
April 27-May 1, 2015	NIH/Ft. Detrick	6.06%	6.82%	9.85%	77.27% (28.79%)
April 28-May 2, 2014	NIH/Ft. Detrick	3.74%	12.15%	10.28%	73.83% (24.30%)
April 1-5, 2013	UTMB (pilot)	6.06%	24.24%	37.88%	31.82% (16.67%)
Average	All	**6.59%**	**12.45%**	**18.85%**	**62.11% (22.80%)**

Faculty Affiliation

- Battelle Memorial Institute
- Biomedical Advanced Research & Development Authority (BARDA)
- Center for Disease Control (CDC)
- Colorado State University
- Data Sciences International (DSI)
- FDA (OCET, CDER, CBER, ORA, OCTEC, CVM)
- MRIGlobal
- National Biodefense Analysis and Countermeasure Center (NBACC)
- NIH (NIAID, NIAID IRF)
- Office of Laboratory Animal Welfare (OLAW)
- Office of the Assistant Secretary for Preparedness & Response (ASPR)
- Public Health England
- U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID)
- U.S. Department of Agriculture (USDA)
- U.S. Department of Defense (DOD)
- University of Maryland
- University of Texas Medical Branch at Galveston
- The World Health Organisation (WHO)

FEEDBACK

Face-to-Face Course Comments

- *"The collection of knowledge from the government and industry compiled for this course is unparalleled. For those who work with developing MCMs this is the most relevant training course that I have ever seen"*
- *"I think it is valuable for policy makers to understand the limitations scientists face in high-containment environments and for scientist to understand the key issues that drive policy making in the MCM mission space"*

Online Course Comments

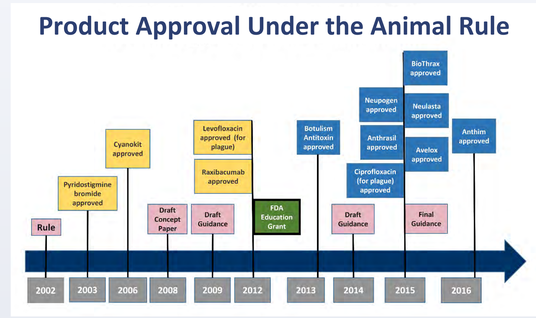
- *"One of the best GLP courses/training I've gone through. New slides with updated information and examples made it very informative even though I am familiar with GLP"*
- *"Overall, the course was logically organized and separated into small modules which enhanced learning. I thought the content was of high quality"*

2017 Evaluation Questions	Strongly Disagree	Disagree	Don't Know	Agree	Strongly Agree
The content and learning material addressed a need or gap in my knowledge or skill.	(0)	(0)	(1) 2.86%	(6) 17.14 %	(28) 80.00%
This activity increased my confidence.	(0)	(0)	(2) 5.71%	(12) 34.29%	(21) 60.00%
This activity will improve my performance.	(0)	(1) 2.86%	(2) 5.71%	(8) 22.86%	(24) 68.57%
This activity will improve patient/public health outcomes.	(0)	(0)	(6) 17.14%	(10) 28.57%	(19) 54.29%
If given the opportunity, I will apply the knowledge gained as a result of attending this activity.	(0)	(0)	(1) 2.86%	(6) 17.14%	(28) 80.00%
2016 Evaluation Questions	**Strongly Disagree**	**Disagree**	**Don't Know**	**Agree**	**Strongly Agree**
The content and learning material addressed a need or gap in my knowledge or skill.	(0)	(0)	(2) 7.41%	(13) 48.15%	(12) 44.44%
This activity increased my confidence.	(0)	(0)	(2) 7.69%	(11) 42.31%	(13) 50.00%
This activity will improve my performance.	(0)	(0)	(3) 11.11%	(11) 40.74%	(13) 48.15%
This activity will improve patient/public health outcomes.	(0)	(0)	(3) 11.11%	(14) 51.84%	(10) 37.04%
If given the opportunity, I will apply the knowledge gained as a result of attending this activity.	(0)	(0)	(0)	(10) 38.46%	(16) 61.54%
2015 Evaluation Questions	**Strongly Disagree**	**Disagree**	**Don't Know**	**Agree**	**Strongly Agree**
The content and learning material addressed a need or gap in my knowledge or skill.	(0)	(0)	(1) 2.78%	(14) 38.89%	(21) 58.33%
This activity increased my confidence.	(0)	(0)	(2) 5.56%	(16) 44.44%	(18) 50.00%
This activity will improve my performance.	(0)	(0)	(2) 5.56%	(15) 41.67%	(19) 52.78%
This activity will improve patient/public health outcomes.	(0)	(0)	(8) 22.86%	(14) 40.00%	(13) 37.14%
If given the opportunity, I will apply the knowledge gained as a result of attending this activity.	(0)	(0)	(0)	(13) 36.11%	(23) 63.89%
2014 Evaluation Questions	**Strongly Disagree**	**Disagree**	**Don't Know**	**Agree**	**Strongly Agree**
The content and learning material addressed a need or gap in my knowledge or skill.	(0)	(1) 2.50%	(3) 7.50%	(19) 47.50%	(17) 42.50%
This activity increased my confidence.	(0)	(1) 2.50%	(4) 10.00%	(15) 37.50%	(20) 50.00%
This activity will improve my performance.	(0)	(1) 2.50%	(5) 12.50%	(13) 32.50%	(21) 52.50 %
This activity will improve patient/public health outcomes.	(0)	(1) 2.56%	(5) 12.82%	(13) 35.90%	(21) 48.72%
If given the opportunity, I will apply the knowledge gained as a result of attending this activity.	(0)	(1) 2.50%	(1) 2.50%	(16) 40.00%	(22) 55.00%
2013 Evaluation Questions (Pilot)	**Strongly Disagree**	**Disagree**	**Neutral**	**Agree**	**Strongly Agree**
The content and learning material addressed a need or gap in my knowledge or skill.	(0)	(0)	(2) 6.90%	(12) 41.38 %	(15) 51.72%
This activity increased my competence.	(0)	(0)	(1) 3.45%	(12) 41.38%	(16) 55.17%
This activity will improve my performance.	(0)	(0)	(0)	(13) 44.83%	(16) 55.17%
This activity will improve patient/public health outcomes.	(0)	(0)	(5) 17.24%	(12) 41.38%	(12) 41.38%
If given the opportunity, I will apply the knowledge gained as a result of attending this activity.	(0)	(0)	(0)	(7) 24.14%	(22) 75.86%

Face-to-Face Course Evaluation Results 2013-2017

Impact

Product Approval Under the Animal Rule



- 66.7% of products approved via the Animal Rule (AR) pathway were approved after course initiation
- 80.0% of products for high consequence pathogens approved via the AR pathway were approved after course initiation
- 269 registered attendees from 2013-2017
- 94% of the participants indicated they would recommend the course to a colleague (2017)
- 96% of respondents indicated they would like to attend the course again in the future (2016)
- The *Product Development Under the Animal Rule Guidance Document for Industry* was released as a final document in October, 2015 (HHS FDA, 2015)

Course Expansion (2017-2022)

On June 26, 2017 the FDA announced their intention to accept and consider a single source application for an award to UTMB that allows for the continuation and expansion of this education program. During the next grant funding cycle (2017-2022), the education program will continue to support the goal of providing a robust, collaborative educational program using problem-based learning techniques designed to bring researchers and regulators together to educate each other on the challenges related to nonclinical and clinical trial studies conducted in maximum containment environments and to identify solutions that are acceptable from both scientific and regulatory perspectives. The expansion of the training program, to include Good Clinical Practices to maintain data quality in barrier nursing settings, will include expansion of the on-line course curriculum in order to deliver on-demand distance education to meet the needs of infectious disease outbreaks. Proposed courses will include:

- *Achieving Data Quality and Integrity in Maximum Containment Laboratories* (F2F)
- *Achieving Data Quality and Integrity in Clinical Trials Involving High Consequence Pathogens* (F2F)
- *Good Laboratory Practice (GLP) Basic Training* (on-line)
- *Good Laboratory Practice (GLP) Refresher Training* (on-line)
- *Good Clinical Practice (GCP) Basic Training* (on-line)

Conclusion

Based on the attendance numbers , diversity of participation (by affiliation and area of expertise), evaluation results, and the number of products approved via the Animal Rule pathway, the course has been successful at achieving the objective of cross-educating the MCM community to promote data quality and integrity in maximum containment laboratories.

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References

- *New Drug and Biological Drug Products; Evidence needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible* (21 CFR Parts 314 and 601, **Federal Register**, May 31, 2002).
- *Product Development Under the Animal Rule Guidance Document for Industry* (HHS FDA, 2015).

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