Risk Management in cGMP Manufacturing

By: Mark Leney, PhD

In his iconoclastic book “The Black Swan”, Nassim Taleb recounts a parable concerning a turkey. A farmer feeds a turkey everyday. Months pass. The turkey feels more certain that the farmer’s visits are associated with food. By the third week in November, the turkey is more sure than ever, [given the “accumulation of all the evidence” he pompously assures his buddies] that the farmer is his friend. He has never been so wrong.

No aspects of cGMP manufacturing is entirely free of risk. Identifying, evaluating, and controlling for risk are key elements of the risk management process. Since 1990, an organization rejoicing in the catchy name of The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use has labored to produce agreed standards for drug development, testing, and market authorization. The ICH Harmonized Tripartite Guidelines that this organization continues to produce and refine, reflect the distilled and agreed thinking of the regulatory authorities in the three major pharmaceutical regulatory areas, Japan, Europe and the USA. The approved Harmonized Guidelines have the same status as an FDA “Guidance For Industry”. While we might not be prosecuted for failing to follow them, we’d want to have a really good reason not to. Clumsy titles aside, the content is relevant and accessible and I’d encourage anyone thinking or writing about a cGMP topic, or indeed reviewing one (think SOP, Batch Record, Change Control, Deviation) to keep the resources at www.ich.org in mind and under review. A

Continued page 7

Influenza Vaccination (aka “The Flu Shot”)

By: Heidi Smith, MD, PhD

Flu season is fast-approaching. The disease commonly known as “flu” is caused by the influenza virus. While most people infected with the influenza virus have a relatively mild (though rather miserable-feeling) illness, the virus can cause serious infections requiring hospitalization, even in otherwise healthy adults. In addition, influenza virus causes thousands of deaths in the U.S. each year, primarily in older adults.

Getting the annual seasonal influenza vaccine, otherwise known as the “flu shot,” is the most effective way to reduce the chances you will be infected with the influenza virus — and avoid transmitting the virus to other people at home, at work, or in the community who may be more likely to develop serious complications. In addition, healthy working
“The Flu Shot” contd.

adults immunized with the flu vaccine have been shown to have fewer episodes of respiratory illness, fewer days of sick leave from work and fewer visits to the doctor’s office (N Engl J Med 1995; 333:889).

The influenza vaccine comes in two general forms: an inactivated vaccine (containing killed virus) given by a shot in the arm or a live attenuated vaccine (containing weakened virus) given by a nasal spray. Both contain a mixture of 3 different types of influenza viruses: influenza B and two different varieties of influenza A (H1N1 and H3N2). Some people may experience a low grade fever and muscle aches in addition to arm soreness (if receiving the vaccine as a shot) or runny nose (if receiving the vaccine as a nasal spray) for 1-2 days after vaccination. About 2 weeks after vaccination, a person develops antibodies to the viruses in the influenza vaccine which help protect them from the flu.

This year MassBiologics employees have the opportunity to obtain the inactivated influenza vaccine shot at the Mattapan campus on November 8th (see page 6). If you are unable to get your influenza vaccination at work on November 8th, you may be able to get vaccinated at your doctor’s office, a pharmacy, or at a community vaccination event. The website “flunearyou.org” can help you locate places to get the influenza vaccine in your area.

NHMPP Launches with Enthusiasm

By: Greg Babcock, PhD

It’s been an exciting month in the Product Discovery department. As most of you are aware, the “Next Hundred Million” Pilot Projects (NHMPP) granting opportunity was launched. This collaborative funding opportunity, launched by the UMMS Center for Clinical and Translational Sciences and MassBiologics, is intended to bring together researchers at MassBiologics and investigators across the University of Massachusetts system to develop novel therapeutics. Immediately after the announcement of the NHMPP, the Product Discovery department was contacted by numerous researchers from multiple UMass campuses.

I was truly amazed by the genuine enthusiasm from the UMass researchers to collaborate with MassBiologics. A total of 13 letters of intent were generated regarding projects associated with Product Discovery. Multiple faculty members in Product Discovery at MassBiologics were involved in crafting these letters of intent. Teresa Broering, Yang Wang, Leila Sevigny and Greg Babcock were all individually named as investigators on at least two of the proposals. Also, Colby Souders was critical in formulating some of the proposals that were submitted. Additionally, I am happy to report that the investigators from the UMass system represented the Medical School in Worcester as well as the Amherst and Lowell campuses.

There was a very short time line to put these proposals together and some collaborations came together with less than 24 hours remaining to submit the letter of intent. Overall, this process created significant energy in the Discovery department and I know generated some stress as well. I want to thank everyone involved with crafting and creatively designing these pilot proposals and for their hard work and dedication to making this collaborative effort a success. Soon we will know which projects will be selected for full proposals and I’m sure this process will again generate much energy and enthusiasm. I look forward to the coming month and the further interaction with the fine researchers in the UMass system.
Information Services Department Goal FY 2013

By: John Fitzmaurice

The MassBiologics Information Services Department goal for the 2013 fiscal year is:
“Identify the key business information systems at MassBiologics and develop a three year refresh or obsolescence plan. Take into account current system functionality, potential new functionality, data owner user needs, interoperability, risk, and potential costs.”

So, what are “key business systems”?

Key business systems are those computerized systems that we rely on for our day to day business. We are all familiar with some of these systems – Document Management, Clinical Data Management, Maintenance Management, Laboratory Management, Email and telephone systems to name a few. There are other key business systems in place to manage and protect our data and hardware such as Server Virtualization, Application Publishing, Data Back-up & Archiving, Data Center Cooling and Power Management.

You might consider your home computer a key business system for managing your household for things such as online banking, bill paying, managing your tax data, and communicating with friends and family.

Key business systems are made up of hardware and software. First, the hardware component includes a laundry list of items -desktop computers, laptops, servers, network switches, modems, routers, wireless network appliances, printers, telephones, power management equipment, server room cooling equipment, data back-up appliances, etc.. The software component includes supporting software such as the operating systems and databases as well as the application itself.

Most likely, you have some of the same hardware and software components at your home. (computer, modem, router, printer, operating system, email client, etc.)

Like you, every so often, we have to decide whether or not to upgrade, replace, or retire our hardware and software as they get old or as our needs change. Over time, hardware and software performance can degrade, devices are no longer supported by the vendor, old hardware and software become incompatible with other newer equipment and applications. So we should plan for that.

There is also the occasional failure of older equipment and software to contend with. Of course, it is best to have a plan in place before something fails and there should also be a determination as to how critical a potential failure could be.

For example, while your teenage son or daughter may consider it a “crisis” when the cyan ink runs out on your home printer, losing a hard drive that contained your only copy of your tax data for the last 8 years could present a more important problem.

Like you, we want to keep our systems running as efficiently as possible, minimize downtime, identify and plan for potential failures, and make sure the systems still meet our needs all the time staying within the limits of a budget.
From the Desk of Dr. Mark Klempner

Building Community: What It’s All About

While there are many types of communities, both virtual and based on common geography, they all share a fundamental characteristic: individuals that come together around common interests for their mutual benefit. As a group of individuals who have come together around the mission of discovering, developing, manufacturing to the highest quality, “biologics” that are shown to be safe and effective to prevent and/or treat human diseases (often addressing diseases or populations where there is limited commercial interest) our MassBiologics community has clear and realistic goals. Indeed, all of our “neighborhoods”: discovery, process development, manufacturing and facilities, quality and regulatory affairs, clinical affairs and administration are passionate about and take great pride in their participation in our community. I am a big believer in the idea that communication builds community and is one of the most important elements for a successful and sustainable community. And in the words of George Bernard Shaw “The single biggest problem in communication is the illusion that it has taken place.”

Frequent and varied ways for our community to communicate is a priority. This is the third issue of our newsletter, The Monthly Dose, that I hope will grow and be viewed as one of those vehicles for communication: a place where we can share the news of each of our MassBiologics “neighborhoods”, read about happenings in our community, and learn about ways to engage in our community and our broader UMMS society. Last week we held our first MassBiologics Community Meeting; another opportunity for our community to share thoughts and concerns. I hope we were successful in providing answers to some of the questions that concern us all. And more important, I hope we were successful in providing an open forum for discussion of our common interests. We plan on holding these community meetings every 3 months. Your feedback and suggestions for making our community meetings as valuable as they can be is appreciated. And returning to Shaw, we should not be under the illusion that a monthly newsletter and a quarterly community meeting will assure effective communication. These efforts, while important, cannot substitute for one on one or small group conversations. To that end, beginning November 6th, I would like to invite each of you to share a story and a cup of coffee with me in the cafeteria every other Tuesday morning at 8-9am. After all, building our MassBiologics community is what it is all about.

2012 Road Bowl Walking Challenge: And The Winner Is…. 

The Third Annual Road Bowl Walking Challenge kicked off on October 1, 2012 and finished Friday October 26, 2012. The Road Bowl was a four week walking competition between the 12 schools of the Worcester Consortium of Colleges. Many teams from MassBiologics participated in this event which counted steps for each team as well as converted other activities into steps such as swimming, biking and Zumba. Last year, more than 200 UMass Medical School employees joined teams participating in the Road Bowl. This year’s fitness challenge will included two contests. First, the team with the highest number of team average steps in the Worcester Consortium of Colleges will be awarded a team grand prize of $500 in gift cards. In addition, the remaining schools were eligible for $250 in gift cards to the team with the highest number of team averaged steps per school. Team averaged steps are total team steps divided by number of walkers on that team. The challenge ends on October 26. We are pleased to announce that the “Sneaker Pimps”, one of the teams from MassBiologics, are the overall winner with close to a total of 3.5 million steps and 1700 miles walked. Team members Ghia Gries, Karin Sanborn, Marcia Steger, Jen Royal and Roxanna Cosma beat out over 200 other teams including five other teams from MassBiologics. The other teams were “Walk This Way” with Patrick Walsh, Teresa Donahue, Robert Greene, Lynne Farley and Paul Landolphi; “UMInternationalWalkers” with Peter Ngo, Sarith Phat, Kelso Brown, Yetnayet Ayalew and Larry Jadormio; “Walk Hill Gobblers Team 1” with Brian Booth, Erin Burns, Phoebe Riley, Colleen Fenn and Stuart Nelson; “UM Walk Hill Gobblers Team 2” with Teresa Broering, Naomi Boattright, Elisabeth Boucher, Andrew Crowley and Monir Ejemel and “UM MBL Cellmates” with Kellyann Barrow, Irina Martinez, Rachel Rivera and AJ Devaux.

Congratulations to all the teams from MassBiologics as well as the hundreds of other participants from across all colleges for their hard work. All teams are invited to attend the Road Bowl Closing Ceremony (see attached). This ceremony will be held at the Massachusetts College of Pharmacy and Health Services on Monday, November 5th from 4 to 6 pm.

Sneaker Pimps
COMECC: The power of many
Annual Commonwealth of Massachusetts Employees Charitable Campaign kicks off Nov. 5

October 29, 2012
By Ellie Castano
UMass Medical School Communications

For the price of a cup of coffee per week, you could help a child learn to read. If you brown-bagged it twice a month, you could help a working family discover tax deductions that would save them thousands of dollars. Skip one restaurant dessert and you could even help a senior citizen recover from isolation and neglect. It sounds implausible, but through the Commonwealth of Massachusetts Employees Charitable Campaign (COMECC), you can.

“The COMECC campaign is really a campaign of small contributions making a big difference,” said James Leary, JD, vice chancellor for community and government relations. “By participating in this annual campaign, state employees can choose an amount to contribute—even $2 a month—to the charity of their choice, and really change someone’s life. It doesn’t take a million dollars or even a hundred.”

With more than 1,000 organizations to choose from, COMECC offers something for everyone to support: from small local non-profits to broad national organizations. If you are undecided about an agency to support, you might consider your local United Way chapter, each of which works with area agencies to advance the common good. The United Way of Central Massachusetts (COMECC code: 459588), for example, crafted a strategic plan based upon a far-reaching study of the most pressing local needs and works with volunteers and other agencies to generate solutions to those problems in a coordinated, comprehensive fashion. Likewise, the UMass Memorial Foundation (COMECC code: 111254), supports a broad range of research and education initiatives at UMass Medical School and UMass Memorial Health Care.

“Through larger organizations like the United Way of Central Massachusetts and the UMass Memorial Foundation, which harness the power of many, every contribution, no matter how small, is maximized,” said Leary.

In 2011, COMECC raised more than $1.7 million, which was used to fund literacy programs, community clinics, animal rights organizations, violence prevention, medical research, land conservation, adoption services, and hundreds of other initiatives from the more than 1,000 prescreened non-profits registered with COMECC.

The 2012 COMECC campaign runs from Nov. 5 through Nov. 26. For more information, contact your department administrator or visit the COMECC website.

Donation forms will be distributed to departments at MassBiologics on Monday November 5th. All forms can be completed and returned to Jeffrey Way via interoffice mail. For any questions please call Jeffrey at x4066 or email him directly at, jeffrey.way@umassmed.edu

For more stories from UMASS Medical School, please visit the UmassMedNow page at http://www.umassmed.edu/news
Key Business Systems contd.

So what should your home plan be for the above examples?

Prepare for the “ink crisis” by monitoring printer usage and keeping one set of spare cartridges on hand.

Prepare for the hard drive crash by routinely backing-up your important data on some other system as well as keeping hard copies of your tax data.

So what is MassBiologics’ plan?

During the current fiscal year, the IS Department will be:

Inventorying and evaluating each component of every key business system
Meeting with system stakeholders and together making recommendations based on the component’s age, usage, and functionality
Taking a three year look-ahead so that we can develop a comprehensive plan for replacements, upgrades, and retirements

Extending Half-Life of a Monoclonal Antibody

By William D. Thomas Jr., PhD

The time a monoclonal antibody remains in the blood is sometimes referred to as its “half-life”. It literally means the time it takes for the blood concentration of an antibody to be reduced by half. The half-life varies from antibody to antibody and changes to the half-life of antibodies can be big improvements. For example, an antibody with a longer half-life might reduce the dose required to treat a person, reducing the cost. A very short half-life for a diagnostic MAb that is used to image cancer could also be an advantage. MAbs with a longer half-life could potentially be used instead of vaccines to avoid potential side effects that some vaccines have.

The half-life of antibodies in the blood can be affected by several factors. The binding of antibodies to the neonatal Fc receptor (FcRn) is known to extend the half-life of IgG1 antibodies. This works by antibodies being engulfed by epithelial cells that then bind to FcRn so they can be recycled back into circulation. Changes to the amino acid sequence of antibodies that affect FcRn binding have been shown to change their half-life. Glycosylation has been shown to extend the half-life of other therapeutic proteins, so it is likely that glycosylation of MAbs can also affect their half-life. Other post-translational changes of antibodies may affect how long MAbs remain in the blood. Antibody characteristics like overall charge (pI) or amino acid modifications like cyclization of glutamate to pyroglutamate may affect half-life too. Changes in cell lines and culture conditions are known to impact glycosylation and other protein modifications.

MassBiologics has studied several MAbs in people and have determined their half-lives. In process development, we will attempt to correlate our cell lines, cell culture conditions and purification procedures to enrich for longer half-lives for our MAbs.

Flu Shot Clinic on November 8th

Stay Healthy This Winter With A Flu Shot...

With flu season just around the corner, we want to remind you that getting a flu shot each year is the best way to protect yourself against the flu! To make sure you don’t become part of this year’s flu epidemic, take advantage of the MassBiologics of UMass Medical School’s flu shot clinic that is offering flu shots to all employees.

Cost: The flu shot is free.
Where: Mattapan Building #1
        Rm. #2002 and #2003
Date/Time: November 8, 2012 (Thursday)
          8:30 a.m. – 10:30 a.m.
          (Note: First thing in the morning is typically the busiest time)
Questions: Contact Jeff Way at 617-474-4066 shot.
Risk Management in cGMP Manufacturing contd.

series of ICH Guidelines address quality topics, and in a rare flash of brevity, these are named Q1 through (currently) Q11. Of interest here is “Q9” the harmonized guideline on quality risk management.

Much of the Q9 guideline is most applicable to drugs that are in the early stages of their life cycle. Our Td vaccine, licensed in 1970, is clearly not in the first flush of its youth. We should certainly be looking to the ICH Guidelines as a method within which we can construct a science-based quality framework on which we can develop new investigational (IND) drug programs, but risk management is something we can apply retrospectively to a vintage product like Td, as we manage change and deviation, or even as we work to maintain consistency through the years. There are many accepted methodologies to achieve risk management and at MassBiologics we are not dogmatic about how we do it. However, at the core is the idea that risk to patients is minimized. Each substantive GMP activity should consider, briefly, or in depth, as appropriate, how the critical quality attributes, or critical process parameters that assure them might be impacted. An example of a critical quality attribute for Td vaccine would be, adequate tetanus immunogenicity – something we achieve by putting the right amount of a suitable tetanus toxoid, with adjuvant, into the final vial, and something that we assure by executing a potency assay prior to the release of each lot. A critical process parameter might be the positive pressure within a system held sterile prior to use, because that system’s integrity is an aspect of the assurance that another critical quality attribute, sterility, is also achieved. Not everything GMP is critical, and recognizing how and where this is the case requires discussion and agreement – it’s all part of the risk management process. We can evaluate risk by examining the likelihood of an occurrence and the severity of the harm that might result. We can control for that risk by mitigating it, typically through a reduction or detection activity. Ultimately we need to know and accept where the residual risk is, talk about that residual risk and keep an eye on it as we manage change or stasis in our GMP systems. A key pitfall to avoid is the conceit that “there is no risk”. When I read that, and I do see it written, I know that the writer has taken a shortcut somewhere in the pathway of risk management that progresses from risk identification through evaluation, control, acceptance and communication. There are always residual risks and we need to get to acceptance and communication of risk based on layers evidence. It is very rare that a single factor, such as “we tested it” is sufficient, without (for example) a solid theoretical basis for expecting the “test” result and a rationale for the reliability of the “test” method.

This has all been a bit theoretical – let me share a useful statistical shortcut with you. In 1983, a couple of Canadian epidemiologists, Jim Hanley and Abby Lippman Hand, published a paper under the elegant title “If nothing goes wrong, is everything alright?” They explored the problem of communicating the risk level for events that have not been observed in a particular data set. If fifty patients in a drug trial show no side effects how sure are we about the frequency of side effects in future patients? How sure can we be about a risk that we have not observed? Because the natural logarithm of 0.05 is very close to 3 (don’t think about it too hard) then an excellent estimate of the upper 95% confidence interval for the true long term frequency for a rare event, never yet observed in a number of observations (N), is given by 3/N. This means, if we have just tried something three times and it has not failed, that simply as a result of seeing zero failures in three trials, we know almost nothing about the long term failure rate. If we have thirty observations and have still to see a failure, we can be about 95% sure that the true failure rate is less than 10%. We’d need to have over 60 patients without a given side effect before you can say with 95% certainty that the true side effect rate is less than 5% and even after 3000 negative tests, without some accessory rationale to reinforce your conclusion, the raw data still only allows you to conclude that the true positive rate is less than 0.1%. This “rule of three” is a neat bit of math, but my point is more fundamental – risk management has to be more than asserting that it hasn’t happened... that just means that it hasn’t happened yet. Remember the turkey and enjoy your Thanksgiving.
In Our Next Issue……

Our next issue will be released in early December.

Department News: Catch up on the latest developments across the organization with updates from your Deputy Directors.

From the Desk for Mark Klempner, MD

Inclement Weather Notifications

COMECC update

Plus Much more...

Contest Winner! Name the Newsletter

Our newsletter has been named! Dozens of names were proposed for our monthly newsletter and one stood out; The Monthly Dose.

The Monthly Dose describes the frequency and our mission. As you know together we are working hard on our next hundred million doses.

Congratulations goes out to Jeff Way who submitted the title and our award recipient. Read next month’s issue to hear about his prize.

MassBiologics HRDI Calendar - November 2012

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<td>HRDI Onsite: Karin Fitch Employee Relations</td>
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<td>Veterans Day Holiday</td>
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