Study Highlights Flawed Dissolution Testing Procedure

New research work at Rutgers University (Piscataway, NJ) may dramatically impact established industry practices and standards for dissolution testing. A group (Joseph Kukura, Jennifer Baxter) led by Fernando Muzzio, PhD, Director, New Jersey Particle Processing Research Center of the Department of Chemical and Biochemical Engineering, has presented data indicating that differences in hydrodynamic effects corresponding to the relative position of test tablets in test vessels are a likely cause for the high variability often observed in dissolution testing using USP Apparatus II.

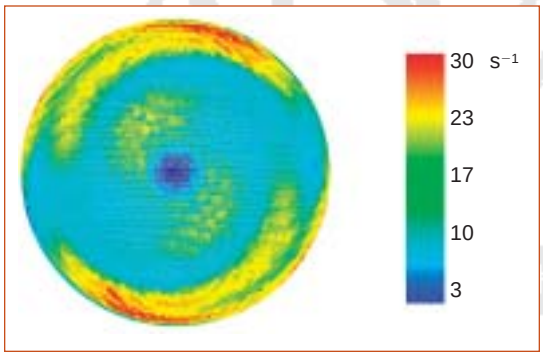

Figure 1 shows shear stress along the walls of the dissolution device at a condition corresponding to agitating an aqueous media at 50 rpm. Regions of high shear are depicted in red, while regions of low shear are shown in dark blue. The computational model was validated through comparison with nonintrusive, experimental techniques including particle image velocimetry to verify the two-dimensional flow field, and laser induced fluorescence to compare the evolution of mixing patterns and species transport.

The results indicate that tablets or tablet fragments which might move during the dissolution test would likely experience high variations in shear forces and, therefore, produce dramatically different dissolution rates. Says Muzzio, "such variations would likely contribute to intrinsically high variability and non-reproducibility of the test for dosage forms where dissolution is mass-transfer limited."

Using a computational model to simulate the flow field, the Rutgers team measured shear forces as a function of tablet position within the USP II vessel. Shear forces control the thickness of the boundary layer available for mass transport and, as observed by Muzzio, "mass transport is the ultimate bottleneck controlling how quickly a drug leaves a unit dose and enters the surrounding medium, i.e. the dissolution rate." As shown in Figure 1, the center of the test vessel, where a tablet is most likely to remain during the dissolution test, experiences very low shear, while regions further away from center see increasingly higher levels.

The researchers also conducted dissolution experiments in which the position of test tablets was carefully controlled. Prednisone calibrator tablets (USP Lot LO0C056) were evaluated at two locations, the dish center and a position 2 cm from center. Results showed dissolution rates at the off-centered position to be more than twice as rapid as those at the center position (see Figure 3).

The implications of the Rutgers experiments are far from inconsequential in an industry where tighter and tighter regulatory requirements are being imposed on testing processes, validation, and documentation. As noted by Muzzio, FDA requires industry to conduct dissolution testing on every batch of product produced. "And, when you have a situation where a test tablet

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Needle-Free Flu Vaccine Hits Pharmacy Shelves

The first influenza vaccine administered as a nasal mist rather than injection in the US will be available this month at national and regional pharmacies. The arrival of "FluMist," in time for the 2003–2004 flu season marks the next turn in a long R&D road for manufacturer, MedImmune, Inc. (Gaithersburg, MD).

FluMist was approved in June 2003 by FDA for the prevention of disease caused by the influenza A and B viruses in healthy people aged 5 to 49. Its approval marked the culmination of a regulatory process initiated with the product's biological license application (BLA) filing in 2000 by Aviron, a biotechnology company that was subsequently acquired by MedImmune. FluMist's availability in the United States for the coming flu season marks an ongoing development effort that spans nearly half a century (see sidebar, "A long development history").

The manufacture of FluMist today traverses facilities in California, Pennsylvania, and the United Kingdom, and is characterized by the quick-turn efforts required to thwart the ever-changing flu. MedImmune Vaccines, Inc. (a wholly owned subsidiary of MedImmune, Inc.) and Wyeth Vaccines (Madison, NJ) jointly market FluMist in the United States. The live virus in FluMist is expected to stimulate a broader immune response than the current vaccine, which contains proteins from inactivated, or "killed" viruses.

According to RxList.com, an Internet drug index, each 0.5-mL dose of FluMist is formulated to contain the following virus strains for 2003–2004: A/New Caledonia/20/99 (H1N1), A/Panama /2007/99 (H3N2) (A/Moscow/10/99-like), and B/Hong Kong/330/2001.

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MEDIMMUNE, INC. AND WYETH VACCINES

Nasal sprayer: FluMist is marketed in a 0.5-mL single dose, prefilled nasal sprayer.

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Vaccine production stands in sharp contrast to the manufacture of chemical pharmaceuticals. For FluMist, the process begins at the MedImmune Vaccines R&D facility in Mountain View, CA, where the master virus strain is created, which is updated every year with the three particular strains that are predicted to be circulating during flu season. The determination of strains is made annually by the FDA and the Centers for Disease Control and Prevention, in conjunction with the World Health Organization.

With the virus strain changing each year, vaccine manufacturers have to be quick on their feet to prepare and distribute large quantities of vaccine in the months between strain determination and flu season. According to James F. Young, PhD, president for research and development at MedImmune, the rate-limiting step is filling. To address this, one tactic MedImmune uses is to make more bulk lots while the filling operation proceeds at its own pace. "It's a question of risk abatement," says Young, explaining that bulk virus can be produced and frozen and put into inventory for later use. "The variable cost in making the virus is small," he adds.

CARY CORTHRON LIGHTHOUSE PHOTOGRAPHY

James F. Young

The master virus strain developed in Mountain View is shipped to a MedImmune facility in the United Kingdom for preparation of the bulk virus lots of each strain. This step of the process, conducted in Speke, outside of Liverpool, involves inoculation of pathogen-free chick eggs with the virus. The eggs are incubated to promote virus replication, and the allantoic fluid of the eggs is then harvested, clarified by centrifugation, and stabilized with buffer to create quantities of the bulk viruses—the raw material of FluMist.

This raw material is then shipped to another MedImmune facility in Philadelphia, where the viral harvests from the three strains are blended and diluted to the desired potency to produce the trivalent bulk vaccine. Each lot is tested, and the bulk vaccine is then filled into the nasal administration device, comprising a glass syringe barrel and PTFE sprayer nozzle. Packaging and distribution follow.

Each prefilled FluMist sprayer contains a 0.5-mL dose. The PTFE tip is equipped with a one-way valve that produces a fine mist of droplets deposited in the nose and nasopharynx.

This intranasal delivery allows the vaccine to capitalize on physiological differences occurring at different sites within the human body. FluMist uses cold-adapted viruses that have been selectively grown over many generations at increasingly cooler temperatures. According to the National Institute of Allergy and Infectious Diseases, the result is a virus that is unable to spread beyond the relatively cool nasal passages and upper respiratory tract to the warmer region of the lungs where disease develops.

Because it is a live vaccine, a cold chain is required. Following filling, the vaccine is frozen at −15 °C or colder and it must remain at that temperature through distribution, being thawed just before use.

In contrast to the US, many international markets have distribution channels ill suited to the sale of frozen vaccines. To address this, MedImmune and Wyeth are collaborating to develop a second-generation, refrigerator-stable version of the product. The liquid trivalent cold-adapted influenza vaccine is now in clinical trials.

For the current flu season, MedImmune is constrained by certain production terms of its BLA. This season it plans to manufacture 4 to 5 million doses. Following the product's initial approval last June, the company submitted manufacturing supplements that will, if approved by the FDA, increase the number of doses that can be manufactured, up to 20 million doses if all the supplements are implemented.

George Miller

A long development history

MedImmune's FluMist is based on technology developed nearly 50 years ago by Hunein "John" Maassab, professor of epidemiology at the University of Michigan School of Public Health.

Maassab began work on an influenza vaccine in the 1950s, doing research funded by the US Army. According to University of Michigan documents, he first isolated the influenza type A-Ann Arbor virus in 1960, and by 1967, he had developed a cold-adapted virus.

By the mid 1970s, NIAID researchers, led by Brian Murphy, M.D., took the lead in developing the live, attenuated flu vaccine. From the early to mid-1980s, researchers applied genetic recombinant technology to produce different recombinant types of cold-adapted and wild strains of the influenza virus.

Wyeth-Ayerst and the NIAID signed a cooperative agreement in 1991 to develop Maassab's live-attenuated, cold-adapted, intranasal-delivered influenza vaccine. That same year, Wyeth completed a licensing agreement, which has since been terminated, with the University of Michigan for commercial use of Maassab's master vaccine strain.

In 1999, Wyeth entered an agreement with Aviron for FluMist marketing. Aviron submitted an application to the FDA for FluMist in 2000, seeking its approval as an annual vaccine for healthy individuals aged 1 to 64. In July 2001, the FDA ruled that the analysis of safety data was incomplete and Aviron continued its efforts. Six months later, in January 2002, MedImmune purchased Aviron and acquired FluMist. In December 2002, the FDA again evaluated FluMist. The vaccine was approved in June 2003 for healthy children and adults ages 5 through 49. MedImmune plans to conduct additional clinical trials to further evaluate the safety and efficacy of FluMist for children younger than 5 and adults 50 to 64.

New CGMP Plant at Purdue University Offers Multiple Benefits

Purdue University will soon break ground on a new CGMP plant that will be used for FDA-approved pharmaceutical manufacturing as well as education. Although it won't open for another year, the new Allen Chao Center for Industrial Pharmacy, named after its principal donor, already has a manufacturing contract. Under an agreement with Eli Lilly and Company (Indianapolis, IN), Purdue will produce drugs to treat multiple-drug-resistant tuberculosis (MRD-TB) as well as teach operators from foreign countries how to manufacture the drugs. The center may also be used to continue the university's research into process analytical technology (PAT).

Preliminary elevation drawings of the Allen Chao Center.

Because the center will be used for both teaching and manufacturing, it will have a U-shaped viewing corridor with glass walls. "Students will be able to see all stages of CGMP manufacturing in action, without interrupting the process," notes Garnet Peck, PhD, Director of the Industrial Pharmacy Laboratory at Purdue. In addition, Rockwell Automation will install touch screens and process-control software that will be used for activities such as electronic notebook-keeping, and the monitors also will visible through the viewing windows. "All core manufacturing facilities have this kind of equipment, but the general public can never see it," adds Joe Stowell, PhD, director of planning for the university's Department of Industrial and Physical Pharmacy. "Here, these processes will be visible."

Some students, once they receive proper training in CGMP procedures, may work as technicians at the site, which will be located at the Purdue Research Park in West Lafayette, Indiana. In addition to supporting the university's regulatory affairs program,Peck comments that the center will also benefit industry by providing students with a stronger practical background. "For example, the students will be better prepared in regulatory issues," he said.

Although the facility was originally conceived to produce small drug quantities for Phase-I and Phase-II clinical trials, the agreement with Lilly expands the center's scope to include finished products. "This could open up a niche for us in orphan drugs as well," notes Peck. "It will be an interesting avenue for our facility." The site will be able to produce 5-10 kg batches of solid dosage forms, starting with capsules and tablets. In addition, Peck believes that the center's services could be valuable for start-up companies that don't have their own production capability and for larger companies who wish to outsource excess capacity. Any income generated from manufacturing at the center will be invested in the university's programs.

Peck and Stowell expect the center will also aid the university's PAT research, including full-spectrum and limited spectrum near-infrared (near-IR) monitoring, and possibly Raman spectroscopy. Purdue began studying near-IR monitoring of fluid-bed drying more than five years ago. The production of finished products at the site may facilitate the PAT studies. Generally, it is more difficult to apply PAT when manufacturing Phase I and Phase II drugs, because at those stages the drug formulations have not been finalized and the processes keep changing. Nonetheless, Peck thinks there may be an opportunity to use PAT at earlier stages. "PAT is so new, that you don't know yet what you could get out of earlier monitoring," he comments.

Under an international program, which also involves the World Health Organization, the Centers for Disease Control and Prevention, the U.S. Department of Health and Human Services, and Harvard Medical School, operators from other countries will come to the Allen Chao Center to receive training in the manufacture of anti-tuberculosis drugs. The aim is to prepare other countries, starting with China, India, Russia, and South Africa, to produce the drugs locally at a lower cost, for domestic use or for export to neighboring countries. More than 400,000 new cases of MDR-TB were reported in 100 countries in 2001. Although the initial quantities of the drug produced at Purdue will use an active pharmaceutical ingredient (API) supplied from a Lilly site in the United States, the ultimate goal is to have the entire manufacturing process completed abroad, including both the API and the finished drug product. Under the plan, the Purdue center will continue to manufacture the drug for the U.S. market, where demand for the drug is small.

Kurt Swanson, project manager with the industrial engineering and construction firm Lockwood Greene, says the design shouldn't pose any particular challenges. "The viewing space adds a layer of complexity, but it's really just another design aspect that you have to consider," he comments. Because a range of products will be manufactured at the site, a lot of flexibility will be included in the facility design. "It's probably not that different than designing a contract manufacturing site," notes Swanson.

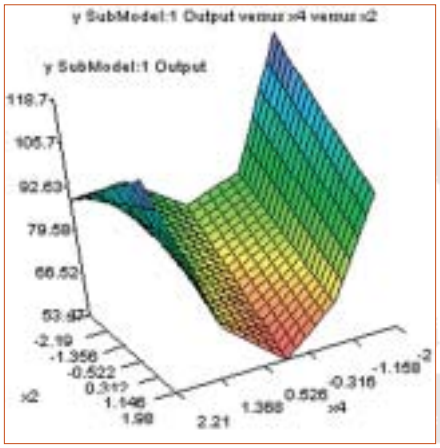
Lockwood Greene has been awarded the contract for the conceptual and preliminary design work. Once the plans are finalized, an engineer-procure-construct contract will be awarded. The university expects to start construction on the site by the end of the year, and they hope to have it up and validated by September or October of 2004.

Laura Bush

New Neural Technology Accelerates Formulation Development

Just about any formulation scientist will tell you it's a challenge to develop cost-effective product formulations without performing extensive trial-and-error research. A new artificial intelligence software package, however, may now offer a solution to this problem.

Developed by Intelligensys (Billingham, Teesside, UK), "FormRules" software is intended to provide time and cost advantages over traditional statistical techniques in formulation development. "If you don't have a good understanding of your system, FormRules uncovers relationships in your data more easily and quickly than if you used statistics," says Intelligensys Product Director Elizabeth Colbourn. Commercial Director Neil Robertson agrees that scientists developing new formulations are not always clear about the cause-and-effect relationships within their systems and run the risk of missing an underlying trend. "Many research groups have a lot of information, but they don't know what the key variables are within their formulation systems," he says.



An example of a graphical display of data that can be produced by Intelligensys's FormRules software.

FormRules incorporates the pattern-recognition capabilities of neural networking and the intuitive language of fuzzy logic to create a unique "neuro-fuzzy" technology. The software learns models that fit a given data set and uses statistical criteria to choose the best model for further testing. Once the model is selected, the software graphically displays clear "if . . . then" rules together with associated confidence levels, enabling users to adapt formulation strategies and direct future experimentation.

FormRules can be used in conjunction with another Intelligensys product, "INForm," to develop customer-specific optimal formulations. INForm helps formulators explore "what if" changes to ingredient quantities and process conditions. Both programs are Windows and network compatible, enabling information to be shared with clients and colleagues.

To validate the technology, Intelligensys conducted a rigorous, 18-month test and development process. The program was tested on a variety of applications, including mathematical functions, tablet film coatings, and immediate and

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can dissolve up to twice as fast, just based on a 1-2 cm variation in placement, this raises significant issues." In fact, there are cases where inconsistent dissolution test results have triggered in-depth product re-evaluations or even complete reformulations.

Although USP can't yet comment on the specifics of the Rutgers findings, Eric Sheinin, PhD, USP VP of Standards and Information Development, says there are a number of established procedures within USP for addressing these issues.

Sheinin says information would likely be first presented to the USP's Expert Committee on Biopharmaceutics. An article might then follow in *Pharmacopeial Forum* to stimulate industry-wide discussion and/or formal comment, and potentially a revision to the *USP–NF*. According to Muzzio preliminary meetings have already been held with USP to discuss possible collaborative efforts. The first formal step in the process, however, would be to submit a "request for revision." A guideline is available electronically on the USP web site (www.usp.org).

A possible complication in the process is that USP is currently in the midst of harmonizing the dissolution chapter of the US formulary with both the European and Japanese pharmacopeia. The Pharmaceopeail Discussion Group, made up of members from all three pharmacopeias, has agreed that once a general chapter has been harmonized, no individual pharmacopeia would unilaterally make changes. The current plan calls for a harmonized document to be approved by early next year.

Meanwhile the Rutgers team is planning follow-up research to characterize the unit dose forms likely to be most vulnerable to this kind of test variability. "We want to first isolate unit dose problems from test problems," says Muzzio. "After that, we'll try to introduce modifications to existing tests as well as help develop new test methodologies that won't have these problems."

John Haystead

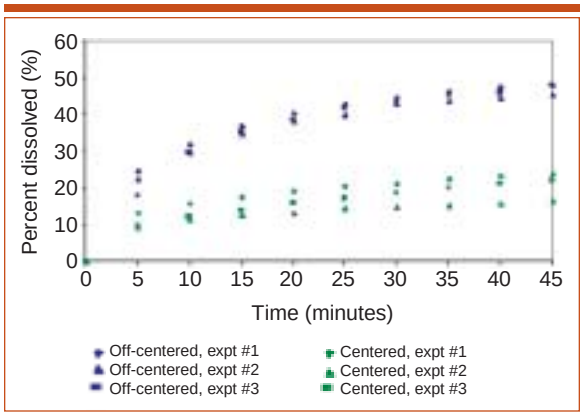

Figure 3 shows the dramatically different dissolution rates measured at different tablet positions. To establish sufficient repeatability, the tests were repeated three times for each tablet position. While some experimental error was observed between runs at each tablet location, the measured dissolution rate variation is apparent and cannot be attributed to error.

controlled released tablets. According to Colbourn, "the product accurately delivered expected results when tested on known, well understood problems." In one case, the software was tested on published catalyst formulation data. Where basic statistical analyses did not reveal any strong relationships, FormRules was able to discover correlations and uncover more information about the formulation.

Already in use at a number of pharmaceutical companies, Robertson says they're seeing a change in the structure of formulation teams with less experienced formulators able to develop good formulations in a short amount of time. "We're now beginning to see a lot of young researchers who can act as anchor points within their formulation teams," Robertson says.

Intelligensys is currently evaluating other applications for the software. "We think there will be a need for us to look at data management issues, specifically for companies that don't have good database structures," Robertson predicts. Colbourn adds that FormRules could also be used to develop expert systems, computer programs that "make decisions" based on rules built by human experts. "The rules that FormRules extracts could be used in lieu of those produced by human experts," she says.

Kaylynn Chiarello