



VOLUME 1/2006

# MICRO NEWS

## MICROBIAL INGRESS

Bryan Wilson, *Study Director*

The Food and Drug Administration (FDA) has recently published a new guidance document to assist the pharmaceutical industry in preparing premarket notification (510(k)) submissions for intravascular (IV) administration sets and accessories, (Intravascular Administration Sets Premarket Notification Submissions [510(k)] Document issued on: April 15, 2005).

The 510(k) guidance document includes information on submissions for Class II devices such as:

- Extension sets
- IV stopcocks and manifolds
- In-line filters
- Flow regulators
- Fluid delivery tubing
- Vial adapters
- IV transfer sets
- Subcutaneous administration sets
- Blood administration sets
- Transfusion filters

The 510(k) guidance references five test methods including Bench, Microbial Ingress, Simulated Clinical, Sterilization, and Biocompatibility testing. Many of these procedures are available to you through Nelson Laboratories, Inc.; this article, however, addresses Microbial Ingress testing exclusively and is written as a summary of comments on the 510(k) guidance document.

### MICROBIAL INGRESS TESTING

The use of a needleless device with a reflux valve or pre-slit septum may, according to the FDA, “increase the patient’s risk of infection because these features allow the entry of microorganisms into the sterile fluid path”.

It is recommended that microbial ingress testing be performed under extreme use conditions, such as repeated insertions into the female Luer or pre-slit septum and static insertion over a period of hours. This testing is intended to simulate repeated access to the same patient with the same IV administration set in place.

Testing should be designed to simulate the use of the device in a clinical setting. Testing should also demonstrate that disinfection procedures used are effective for removing microorganisms from the device.

At Nelson Laboratories, Inc. we have developed protocols for this type of testing and are able to modify them to meet our customers’ specific needs. According to the 510(k) document, each of the following items should be included in the protocol with modifications for time, number of devices, or other procedures that replicate the clinical setting for a device. These points have been taken from the 510(k) Guidance document:

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- Use positive and negative controls in the study.
- Provide rationale for the sample size used in the study (we are suggesting at least 24 each of your device and the control device).
- Show validation (using microbiological techniques) of the disinfecting procedures for insertion and reinsertion into the needleless access site.
- Use sterile, finished product for testing.
- Inoculate the sample surfaces with 10–20 microliters of a suspension containing a minimum of 10<sup>3</sup> colony forming units (CFU) of bacteria commonly associated with skin or IV line contaminants (such as *Staphylococcus aureus* or *Staphylococcus epidermis*).
- Allow the inoculated surface to dry for one minute.
- Disinfect the inoculated surface with 70 percent isopropyl alcohol (IPA) and allow to dry.
- Access with a needle or blunt cannula attached to a syringe.
- Repeat the process at least five times over a period of at least 24 hours. After the final access, inject growth media into the septa and count the microorganisms passing through the septa.
- Test positive and negative samples concurrently.

For more information regarding Microbial Ingress testing or other tests mentioned in this new 510(k) Guidance document please contact us at [sales@nelsonlabs.com](mailto:sales@nelsonlabs.com).

Let us  
know  
how  
YOU  
feel.

Nelson Laboratories is known for excellent customer service and technical expertise. We know this because of the feedback we receive from you, our customers. By staying in touch with the needs and wants of our diverse clientele, we are able to maintain the highest quality in customer service and testing.

Let us know how you feel about your experience with Nelson Laboratories. Each customer has the opportunity to fill out a customer feedback card. The feedback card is sent with the final report and can be returned by mail or filled out online at [www.nelsonlabs.com/secure/cssurvey.jsp](http://www.nelsonlabs.com/secure/cssurvey.jsp) For matters that require more prompt attention feedback can also be sent directly to [feedback@nelsonlabs.com](mailto:feedback@nelsonlabs.com).

Because we feel your feedback is so important, our customer service team reviews each comment to determine where we are succeeding and where there is room for improvement. At Nelson we are also very open to sharing the comments, names excluded, with our customers upon request. If you have any feedback for us please visit our website to fill out the feedback form or send a direct email. We are looking forward to hearing from you and getting your feelings about Nelson Laboratories.

*The study directors are very helpful. I also appreciate the guidance that I get from the experts at Nelson Labs, i.e. Dr. Nelson and other who provide advice.*

*Great people. Nice to work with to solve our problematic assays.*

*Overall, Nelson Labs provides a good product. You seem to stress a helpful friendly staff.*

*The service and communication with the lab was excellent giving me confidence that the testing was going to be completed timely and accurately.*

*Great customer care: Love the online checking of reports.*

*The quality and professionalism of your employees. Excellent communication and updates.*

*The courteous treatment received from all your employees.*

*Timely test results and reports. Excellent customer service support.*

*Quick turn around time and friendliness of staff, great job.*

*Extremely thorough, professional results and communication always in a timely manner.*

*Everyone is always ready to help to resolve any situation.*



The ASTM F 1671 viral penetration study evaluates the viral penetration resistance characteristics of protective clothing materials using the  $\Phi$ X174 bacteriophage. It was designed to comply with the ASTM F 1671 procedure developed by the ASTM Subcommittee F23.4 on Biological Hazards. The protective clothing materials tested are intended to provide protection against blood, body fluids, and other potentially infectious materials. The three main blood borne pathogens this test is concerned with are the hepatitis B virus (HBV), hepatitis C virus (HCV), and the human immunodeficiency virus (HIV).

Nelson Laboratories, Inc., (NLI) was a key contributor in the development of the ASTM F 1671 method. In 1990, NLI was asked to prepare the initial draft test procedure to be submitted to the ASTM F23.40 subcommittee on Biological Hazards, in conjunction with other industry experts. This opportunity allowed Nelson personnel to develop an in depth understanding of the step by step procedure and intricacies of the test. As the demand for testing increased, we took steps to ensure our testing environment was of the highest possible quality. Some of these improvements include testing within a HEPA filtered clean bench, testing under controlled temperature and humidity conditions, and performing qualifications for each technician involved in the testing. As a result, we have helped set the standard for quality barrier testing and continue to be recognized as one of the premier ASTM F 1671 test laboratories in the world. Because this testing

is so important to our clients, scientists from NLI continue to be actively involved with this ASTM Subcommittee.

The ASTM standard requires a compatibility test be performed for each product type. This test is performed to determine what effect, if any, a material may have on the virus, and/or the E. coli host. Some materials may cause inactivation of the E. coli host or virus and may not be suitable for testing. Demonstration of product compatibility is a key variable and should never be ignored. Even slight changes in product components may affect compatibility; therefore, NLI recommends repeating compatibility testing with any product change. Based on the compatibility ratio of a product type, the concentration of virus used in the test is adjusted to the appropriate level. This will ensure an adequate limit of detection for any penetration. Nelson Laboratories offers compatibility testing with every ASTM F 1671 test submitted. We consider this a necessary element in providing results our clients can rely on.

Because the products tested with the ASTM F 1671 method are intended to provide protection against blood and body fluids, the surface tension of the test medium must closely mimic these fluids. A surface tension of 40-44 dynes/cm simulates the wetting characteristics of blood and body fluids. At Nelson Laboratories, the surface tension of each lot of medium is verified prior to being released for use in the laboratory. This is another way NLI helps ensure consistency for our clients.



## VIRAL PENETRATION – ASTM F 1671

Our capacity is another reason to select Nelson Laboratories. We are currently able to test up to 40 samples per day, and do so on a regular basis (an FDA submission requires 32 samples to achieve an acceptable quality level (AQL) of 4%). The flexibility to accommodate your deadlines is not the only advantage of our capacity, we also work with a broad diversity of samples and sample related challenges. This experience can be an essential asset for our customers as they plan, execute, and interpret their testing.

As you can see, we take this test very seriously. We know you need consistency and reliability in your testing, and we have taken the extra steps to provide you with the assurance of quality. If you have any additional questions, or would like to discuss this test in greater depth, please feel free to contact one of our highly trained technical staff.

### NELSON NEWS

Nelson Laboratories will be participating in a interlaboratory study to determine the reproducibility and bias of ASTM Standard F2459-05, published August 2005. This standard has been developed for the gravimetric analysis of extractable residue from metallic medical components.



# Biocompatibility Testing

By Thor Rollins, Study Director

Biocompatibility testing is very common in the medical device industry. With 24 categories under which a device could qualify, the biocompatibility testing experience can be intimidating. Each category has a unique set of testing requirements, and even after a device has been categorized, a myriad of decisions for each test remains. Although this process can be difficult, working closely with a testing facility and regulatory agency may help eliminate surprises that can drain resources and time. The biocompatibility team at Nelson Laboratories, Inc., can help you in developing a comprehensive testing plan.

There are three basic tests every medical device must be subjected to: cytotoxicity, sensitization, and irritation. Each test screens for the presence of toxic, leachable materials. Based upon the category of the device, as many as five additional different testing categories may also be required.

Occasionally, a product will fail a test. However, this

does not mean the end of the line for that device. We can help you determine the cause of a failure and what steps to take next. A failed result may be due to a single component. In order to understand this, we recommend component testing of any failed product. The MEM elution test is an inexpensive and reliable way to identify potential component issues. By identifying potential component issues early in the process, companies can save money by preventing costly retests or delays on the more expensive and time consuming tests.

If raw materials are ruled out as a cause for failure, the next area to investigate is the manufacturing process where additional leachables may be added to the product. Some of the most common problems are inks or adhesives which have not cured completely and residual detergents on the device. Residues can also be added during the sterilization process.

If the raw materials and the manufacturing process are

Medical devices which contact circulating blood may cause blood cell damage through chemical or physical means. A static in vitro hemolysis test is proficient at detecting cell damage due to chemical interactions but can not accurately predict the amount of blood cell damage caused by physical means for devices which recirculate blood. A modification of the standard in vitro hemolysis tests can be performed that will mimic the actual use of the device and thereby can examine both factors that may cause blood damage.

The device is attached to a mock circulatory flow loop composed of a blood reservoir, non-hemolytic tubing, and a peristaltic pump. The medical device is attached to the tubing. Physiological saline is run through the loop to rinse the surfaces of the circuit. Anticoagulated bovine blood is then used to prime the loop. Blood is then circulated from a reservoir, through the loop for a short time (5 minutes) then a first blood sample is withdrawn. Blood

circulation then continues for several hours with blood samples taken periodically. A control loop (flow loop without the device in place) is then tested using the same blood pump to establish a baseline reading of hemolysis caused solely by the pumping of the blood. The blood samples are tested for the presence of plasma hemoglobin which is indicative of hemolysis. The results for the test are presented as a graph of hemolysis vs. time. As there is no standard method at present for in vitro circulating blood hemolysis testing, the manufacturer should test a predicate device (i.e., a

device which has already obtained regulatory approval) side by side with the new device in an identical loop for comparison.

The cost and turn around time for this test is dependent upon the number of samples and the number of sample times. Please contact Michelle Lee or Chad Summers with any specific questions about the test method. For pricing and turn around time quotes please contact [sales@nelsonlabs.com](mailto:sales@nelsonlabs.com).

**IN VITRO  
BLOOD  
CIRCULATION  
HEMOLYSIS**

By Michelle Lee,  
Section Leader



not the cause, a decision must be made whether or not the amount of toxicity is justifiable based on the benefits of the device. A failed test is certainly not the best scenario for submission, but it need not be the end of the road. Biocompatibility testing must evaluate all test results, as a whole, and the relationship to the device, its use, benefits, and risk. A failed test result is more likely to be accepted if higher level tests (e.g., tests which more directly simulate the products use such as functional implant studies) show normal results, and a well supported, risk assessment-based justification can be written.

To support such a justification, test results can be compared with results of similar devices which are already on the market (i.e. predicate testing). In addition, dilutions of the device extract can also be prepared and tested to determine an endpoint for the toxicity. This end point determination provides you with a more quantitative perspective as to the concen-

tration of the leachate.

Of course, the key to a successful biocompatibility testing experience is working with a laboratory that will closely partner with you about all of the details of your testing. Frequent updates and regular communication can help you save time and money and avoid the pitfalls that so many companies experience. It is also essential to have an open and communicative relationship with your regulatory reviewer. Early buy in on your testing scheme seems to always bode well when it is time for final review.

Nelson Laboratories is dedicated to helping customers determine the right biocompatibility test plan, and partnering with our customers throughout the testing process. We welcome the chance to assist you with your biocompatibility testing needs. To find out more about biocompatibility testing with Nelson Labs, please contact Thor Rollins at [trollins@nelsonlabs.com](mailto:trollins@nelsonlabs.com).

## NELSON BIOCOMPATIBILITY TEAM

**THOR ROLLINS:** Thor received his B.S. in biology from Idaho State University. He has been with Nelson Laboratories, Inc. since 2002. He is a registered microbiologist, RM(NRM), with the National Registry of Microbiology. He is a Study Director in the Biocompatibility section where he works with many in vitro tests. Thor specializes in all aspects of the cytotoxicity test and cell culture.

**AUDREY TURLEY:** Audrey started at Nelson Laboratories in 1996. She started in the Bioburden department working with gamma sterilization projects. After five years in Bioburden, Audrey moved over to the Biocompatibility section to assist in bringing up the Chromosome Aberration Assay, which she is now the Study Director over. Audrey received her Bachelors degree in Biology from the University of Utah and is a registered microbiologist with the American Society for Microbiology.

**ANN HAVERKOST:** Ann is the newest addition to our Biocompatibility department. She has a B.A. in Anthropology and is finishing up her M.A. She started here in November 2005 working as the Subcontracting Specialist in Biocompatibility. Ann is in charge of subcontracting our in vivo tests and other tests Nelson does not perform in house.

**CHAD SUMMERS:** Chad has been with Nelson

Laboratories for the past ten years. As a Study Director Chad oversees the Ames Genotox Assays, Hemolysis studies and the Coagulation Analysis. Chad also oversees static Hemolysis testing and can assist in design and development of dynamic blood study protocols using flowing blood which mimic clinical conditions.

**MICHELLE LEE:** Michelle has been working for Nelson Laboratories for 12 years. During this time she has been the supervisor over many tests. She has been the Biocompatibility and Subcontracting Section leader for the past seven years. As Section Leader Michelle oversees all the testing in her section and is the Study Director of the Complement activation testing. Michelle has her Bachelors of Science and is a registered microbiologist, RM(NRM), with the National Registry of Microbiology.

**BRYAN BREZOFF:** Bryan has been working at Nelson for over three years. He has a B.S. in Microbiology from Weber State University and is a registered microbiologist, RM(NRM), with the National Registry of Microbiology. Bryan has worked on many tests including Chromosome Aberration, MEM Elution, Agar overlay, Virucidal Efficacy testing, Micro BCA Protein Assay, Micro Lowry Protein Assay and Biuret Assay. Currently Bryan is the Study Director over Virucidal and Protein testing.



THOR ROLLINS



AUDREY TURLEY



ANN HAVERKOST



CHAD SUMMERS



MICHELLE LEE



BRYAN BREZOFF



## Future Events By Nelson Laboratories

### THE SCIENCE OF STERILIZATION VALIDATION WORKSHOP

Join us for this two day workshop offering an opportunity to understand sterilization methods, microbiological basics and how to validate your sterilization and manufacturing process.

#### TOPICS TO INCLUDE:

Sterilization Basics  
Radiation Sterilization  
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Biocompatibility  
Packaging  
Shelf Life  
Lot Release  
Steam Sterilization

**LOCATION:** Radisson Hotel  
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**DATE:** May 1-2, 2006 • 8:00-5:00

**PRICE:** Before April 7, 2006 - \$600.00,  
after \$650.00

**CONTACT:** Jared Forsyth  
or Clarence Baker at  
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