Compliance Matters

Medical Gas Update

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For medical gas manufacturers June was a notable month. Effective June 1, 2009, new federal Food and Drug Administration (FDA) requirements for electronic registration of drug manufacturing establishments took effect. A few weeks later the US Pharmacopeia (USP) released a draft of the long awaited medical gas monographs for public comment. In this article we will examine the key elements of these new requirements industry compliance managers will face in the coming months.

FDA STRUCTURED PRODUCT LISTING REQUIREMENTS

For an agency traditionally focused on paper records, the FDA's new requirements for electronic registration and drug listing, called Structured Product Listing (SPL), are a significant milestone on the road towards transitioning to a total electronic documentation and record keeping system. Although sending the agency an electronic vs. a paper form seems simple enough, experienced compliance managers know that when dealing with FDA requirements, the devil resides in the details. We have been working with the FDA's new registration process for some time now and find it complex and full of subtle technical details that must be satisfied. Many of these details must be resolved in ways that are not intuitive. Firms without the support of a dedicated IT department, or at least access to someone very knowledgeable about electronic data forms and their transmission, are likely to find this new process daunting at best.

The FDA is moving to SPL for some very basic reasons. First, over the last few decades the management and storage of paper records has morphed into a resource-intensive and cumbersome process. The FDA needs significant resources and time to perform even simple data sorts to get at information they need to effectively manage the safety of the US drug supply. Theoretically, SPL puts this information at their fingertips, making it available almost instantly. The FDA also intends to make this information available to practitioners on their websites. Second, SPL is basically a computer code, not an image file like a PDF document, which makes it an ideal way to store large amounts of information for easy sorting and retrieval. Third, SPL is an open format language, and has been adopted as an ANSI standard as of March 2009. The FDA, as well as drug manufacturers, will therefore not have to pay royalty fees to one specific company to use the basic technology.

The SPL requires that you learn a new language in order to navigate around the process. This includes deciphering technical terms such as Data Universal Numbering System (DUNS) numbers, Global Unique Identifier (GUID) numbers, XHTML forms, SSL Certificates, and Secure Electronic Gateways. If you find sending and receiving emails and surfing the web difficult, these new SPL related issues will require some significant furthering of your computer technology education.

The FDA has adopted the DUNS number as the ID number for a facility. Every business facility in America, as well as throughout most of the world, has a nine digit DUNS number. These nine digits are the equivalent of a social security number for a business location. The DUNS system is administered by Dun & Bradstreet, and if you do not currently have a DUNS number, or do not know what your number is, Dun & Bradstreet will provide that for free. The catch here is that you can only make an application for one site at a time for free, and processing of free applications can take 30–45 business days. This means that if you have 10 branch locations you must file ten applications and wait one to two months. You can shorten this process by subscribing to Dun & Bradstreet's information database service. Having and submitting a DUNS number is a mandatory requirement for the FDA's SPL process, so there is no avoiding it.

There are spaces in the different X Forms where you are required to enter a GUID number. Fortunately, the GUID number, which is a randomly generated 128 bit hexadecimal number, is easier and cheaper to find and use. A simple Google© web search on "GUID Number" will be direct you to various sites that will generate any GUID numbers you need. Downloadable executable file utilities on your computer also will generate GUID numbers, which you can then simply cut and paste into the forms where required. Using GUID numbers is mandatory in the SPL process.

Using the XHTML forms is another mandatory requirement. FDA has contracted with Global Submit *(www.global submit.com)* as the provider of the XHTML, or X Forms, that will be used in the SPL registration and listing process. These can be downloaded for free. Other companies offer their own X Forms for a fee, and these may be easier to use than the FDA's versions. Once you have downloaded the SPL X Forms your web browser needs to be configured or modified with an add-on utility in order to read the XHTML format. Each of the three forms has numerous drop-down menus where information must be entered.

Since these forms were designed for all drug manufacturers to use, there are many items for which medical gas manufacturers will be providing information that previously the FDA had not required gas firms to submit. Rather than submitting a label to the FDA, you now have to embed a digital image of each of your labels in the X Form. For bulk product this will include a copy of your Certificate of Analysis. It is also no longer acceptable when entering package (cylinder) sizes to enter "Various sizes as ordered by Customer." In the new SPL world each cylinder size must be entered separately on the form.

Each form must be run through a software validation process to check for missing or erroneous data. You can do this either before you

send the form to the FDA using a downloadable validation package, or the FDA will run it through the validation process once you submit it, and before they publish it. If there are errors, the FDA sends the submission back to you to track down the error and re-submit. The validation software unfortunately doesn't direct you to where the mistakes may be.

Once you have successfully navigated through the X Form entry and validation process and are ready to send the information to the FDA, you cannot simply attach these files to an email and send them to the agency. To electronically send files to them, you will have to apply for and establish an FDA Electronic Gateway Portal. This involves submitting various documents and certifications to the FDA, setting up the electronic gateway connection along with the requisite SSL certificates, and going through a test and verification process to validate the gateway connection. Also be aware that the gateway will be linked to the one specific computer in your business that was used to establish the link, and there are some specific software configuration requirements for that computer. The smartest approach is probably to use a dedicated computer for the FDA electronic gateway; otherwise you could encounter configuration issues every time you try to connect to the FDA, since most firms will probably only connect to the gateway once or twice a year.

Setting up this process, depending on your level of computer savvy, will involve some significant work and an investment of time and resources. We understand that establishing just the gateway part of the process takes roughly 10–12 work hours spread over three to four weeks. This time commitment assumes you are familiar with the process. Novices should plan on at least double that investment in time.

SPL registration and listing is something that all medical gas manufacturing firms will have to successfully accomplish over the next 6–12 months; the FDA stopped taking paper registration as of June 1, 2009. The good news is that the annual re-registration process is somewhat less painful than the initial registration, provided no changes are needed.

USP PUBLISHES NEW MEDICAL GAS MONOGRAPH DRAFTS

In June, the long anticipated, revised USP monographs were published in the Pharmacopeial Forum as draft notices for public comment. We fully expect that these will be finalized and most likely appear in the USP/NF either early next year, or by midyear 2010. Once the new monographs are published our industry will have roughly six months from that date to be in compliance.

One of the most contentious issues up to this point, the requirement to use USP Reference Standards instead of NIST traceable calibration standards to calibrate medical gas analyzers, appears for now to have been decided in line with input from CGA and other key third parties involved in the discussions, such as B&R Compliance Associates. For the time being the medical gas industry can continue to use NIST certified calibration standards to calibrate medical gas analyzers. However, there are a number of specific changes that will probably require some medical gas firms to purchase new analytical equipment.

For starters, the old burning splint test to identify oxygen and nitrogen is gone. USP saw this test as a holdover from the 1800s and has replaced it with a modern analytical method. For oxygen, the official method to perform ID (as well as assay) testing is now the paramagnetic style analyzer. The old chemical Orsat method is officially

retired. The USP/NF method to identify and assay nitrogen is now the gas chromatograph (GC). Firms that fill nitrogen cylinders using a manifold with nitrogen as the only inert gas connected can still continue to use the paramagnetic method to ID and assay, provided they have a validation study for both the analyzer as well as the fill process. This fill process validation is a new twist on what most firms have been doing up to this point, and it is required to test and confirm that nitrogen is the only inert gas available on the manifold. Unfortunately, when filling nitrogen NF on a manifold with other inert gases such as helium or argon connected, you will now have to use either a GC or a set of validated engineering controls in conjunction with a paramagnetic analyzer to perform ID testing. This handful of changes likely affects the majority of medical gas manufacturers. All the other medical gas monographs except carbon dioxide were updated, and there are numerous technical changes in all of them. If you have specific questions on these monograph changes or the process validation/engineering controls issue mentioned above, give us a call and we would be glad to walk you through it.

The USP made significant additions to the medical gas monographs by adding some general chapters covering analytical equipment operation and validation. It is now mandatory to perform an Installation Qualification (IQ), an Operational Qualification (OQ), and a Performance Qualification (PQ) for both GC equipment and paramagnetic analyzers. This IOPQ is otherwise known as a validation of the analytical equipment. The USP lists a number of specific parameters to be considered during the IOQ phase of the validation, such as system suitability, leakage, sampling techniques, sample flow rates, and environmental conditions. The PQ phase involves calibrating and operating the analyzer to verify it operates as intended within the specified range. The old paramagnetic validations that many manufacturers have are no longer useful, as these typically validated that the paramagnetic analyzer was equivalent to the old Orsat method, and did not address any of the issues set out in the new USP requirements. Keep in mind that this USP validation process must now be performed for each analyzer used. You cannot perform one validation for an analyzer model, like the Servomex 570, and use it for all the analyzers at all your branches. While not an especially onerous process, these qualifications are now a requirement, and firms should expect FDA investigators to be looking for them in the future.

The good news is that the medical gas industry was quite effective in getting the USP to incorporate language on sampling processes, analyzer operation, calibration requirements, and system-setting parameters that are consistent with how manufacturers operate and maintain the equipment today. Most of this guidance in previous issues of the USP/NF had been written by scientists, and often did not reflect the reality of how things operate in the field. The USP is currently reviewing the monograph for CO_2 and is apparently seeking to harmonize the Food Codex and the Drug Monograph for this gas. Our industry will be interested in keeping the beverage grade testing requirements from bleeding into the analytical requirements for medical gases, and we will keep you posted on that process.

Based on these two issues, which will begin to have their full impact later this year and on into 2010, we expect compliance managers in the medical gases industry will have their hands full implementing all the new requirements. Over the last year to eighteen months we have seen relatively little activity with regards to new medical gas regulations, but these new requirements clearly signify that government regulators have not forgotten about the medical gas industry. New regulatory issues are beginning to appear on the horizon, and in future articles, we will keep you abreast of those issues as they develop.

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