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PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2008, Vol. 28 No. 3

A Risk-Based Approach to Cleaning Validation using Visible Residue Limits

by Richard J. Forsyth and Jeffrey L. Hartman

This article describes the development of a Visible Residue Limits (VRL) program in a pharmaceutical manufacturing facility, including sample and viewing parameters. Opportunities for VRL implementation were identified in both pilot plant and manufacturing settings.

Introduction

Before formal cleaning validation programs were instituted, visual inspection was the primary means of determining equipment cleanliness. The use of visual inspection is still typically a component of a cleaning validation program and for routine inspections of cleaning effectiveness, but the use of visual inspection has not been successfully implemented as the sole criterion for a cleaning validation study.

A validated cleaning program based on visual inspections using Visible Residue Limits (VRLs) in conjunction with swab testing is possible. Acceptable VRLs can be established in conjunction with and compared with swab results. Assuming the swab results demonstrated a validated cleaning procedure, if the results are in agreement, then the VRLs may be used going forward. A similar argument has been successfully used to defend the use of rinse sampling established in conjunction with swab results.

The use of only visual examination to determine equipment cleanliness was proposed as far back as 1989 by Mendenhall.[1] He found that visible cleanliness criteria were more rigid than quantitative calculations and clearly adequate. The FDA, in their "Guide to Inspection of Validation of Cleaning Processes," limited the potential acceptability of a visually clean criterion to use between lots of the same product.[2] LeBlanc also explored the role of visual examination as the sole acceptance criterion for cleaning validation.[3] The adequacy of visible residue limits continues to be a topic of discussion.

Visible cleanliness is the absence of any visible residue after cleaning. Although this is a seemingly straightforward definition, a number of factors influence any determination. The most obvious is the observer. Not only the observer's visual acuity, but also training on what to observe, influences the outcome of a visual inspection. The levels of illumination in the inspection areas and shadows caused by the equipment influence what is seen. The distance and the angle of the observer from the equipment surface also have an effect. Finally, the individual residues that comprise a given formulation affect the overall visible residue limit. Fourman and Mullen determined a visible limit at approximately 100 µg per 2 × 2 in. swab area[4] or about 4µg/cm^2. Jenkins and Vanderwielen observed various residues down to 1.0 µg/cm^2 with the aid of a light source.[5]

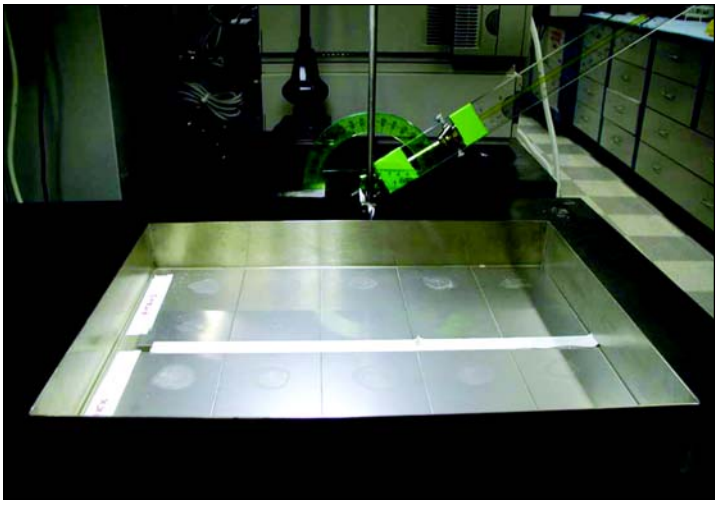

Figure 1. Representative residues on stainless steel.

Control of the parameters that can influence the determination and use of VRLs serve to minimize the subjectivity of the process. Consistent viewing conditions, a trained pool of observers, and solid database of residue VRLs make up a program that can consistently determine visual equipment cleanliness. This approach is analogous to using swabs to

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test for residue or manual cleaning procedures. These processes also have subjective parameters, but by clearly defining the specific procedure for each, both have proven acceptable to the regulatory agencies.

The Acceptable Residue Limit (ARL) for drug residue is often determined on a health-based and an adulteration-based criterion.[5,6,7] The limit used is the lower of the two limits. A health-based limit is generated from toxicity data, which can be expressed as Acceptable Daily Intake (ADI). The health-based limit is calculated using the ADI and the parameters of the equipment used to manufacture the formulation.[6] For the adulteration limit, a carry-over limit of 10 ppm or a baseline limit of 100 µg/swab is often used in the industry. Based on past experience in this facility, if the ADI is <0.1 mg/day, the health-based limit will be lower. The adulteration limit will generally be lower for ADI values >0.1 mg/day. If the visible residue limit could be established, and it was shown to be enough below the Acceptable Residue Limit so that the variability of subjectivity parameters was not an issue, it would be reasonable to use a visible residue criterion for cleaning validation.

For this study, the visible residue limits of Active Pharmaceutical Ingredients (APIs), commonly used excipients, and detergents were determined. Observers viewed residues under viewing conditions similar to those encountered in both a pilot plant facility and a commercial manufacturing facility.

Visible Residue Parameters

Since the determination of a visible residue limit is, to a large extent, subjective, the variables associated with studying visible residue were defined, and then experimental parameters for the study were established. The parameters considered were: surface material, light intensity, distance, angle, residue appearance, and observer subjectivity.[8]

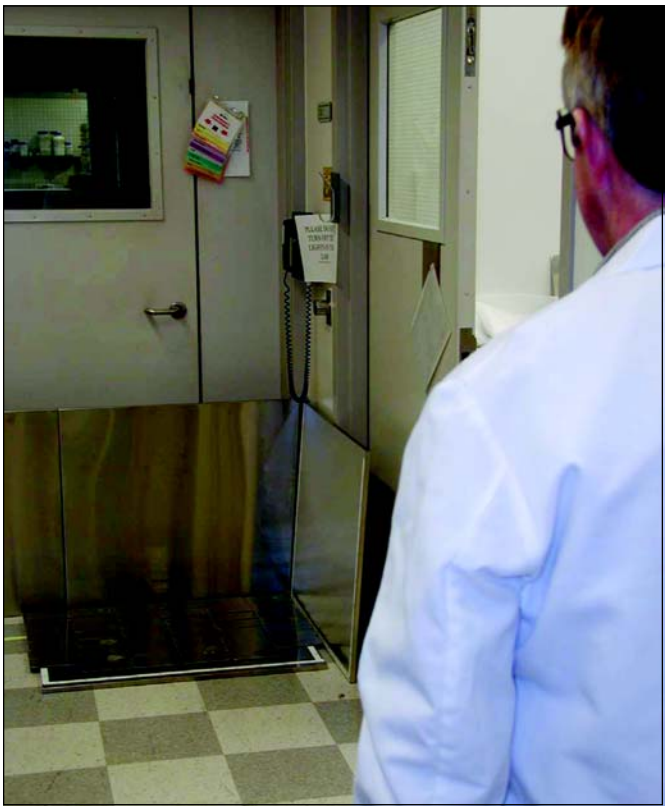

Figure 2. Viewing residue samples.

Stainless steel was an obvious choice for surface material since >95% of manufacturing equipment surfaces are stainless steel. For the purposes of this study, representative stainless steel coupons were used for spotting purposes in the laboratory setting.

The lighting conditions in the manufacturing pilot plant differ from room to room. The light intensity was measured in each room of the pilot plant and the wash area to determine a range of light intensity. For consistency, the light measurement was taken in the center of each room at about 4 feet from the ground. The light intensity ranged from 520 to 1400 lux. To allow for shadows and different positions within a given room, it was decided to conduct the visible residue study between 400 and 1400 lux using a light source directly over the sample. A fluorescent light served as a light source to provide the same type of light that is used in the pilot plant. A plastic cover with different degrees of shading was placed over the bulb and was rotated to adjust and control the intensity of the light. A light meter was used to set and verify the various light intensity levels.

To minimize observer subjectivity, a pool of observers viewed all of the samples. The angle and distance of the observer were considered next. A distance of six to 18 inches from the equipment surface and a viewing angle of 0 to 90° were considered as practical viewing parameters. The first set of spots was prepared and viewed from different distances and angles. The distance did not have a significant effect; therefore, a comfortable viewing distance of 12 inches was chosen. The viewing angle, on the other hand, turned out to be a critical variable. Looking at the spots from a 90° angle (directly over head) was not the optimal angle. Spots were not as easily seen. Having the observer and the light source at the same angle significantly reduced the visible reflectance from the residue. There also was increased reflectance interference from the surrounding surfaces. Decreasing the viewing angle made the spots more visible due to reflectance of light off of the residue. A viewing angle of 30° was chosen although lower angles occasionally provided more reflectance. A 30° angle provided the shallowest practical viewing angle, taking into consideration the surface locations where residues are most likely to be seen in manufacturing equipment, i.e., corners and joints.

The lighting conditions in the commercial manufacturing suites differ from room to room and also depend on equipment size and degree of disassembly for cleaning. The larger size of the equipment in the manufacturing facility provided the greatest difference compared to the smaller equipment in the pilot plant. The increased size deepens the shadows in the interior of the equipment. To compensate for lighting conditions, a portable light is used for inspection as necessary. Therefore, the range of lighting for this study was from 100 lux up to the intensity of the portable light. For the lower lighting level, ambient fluorescent light served as a light

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source to provide the same type of light used in the manufacturing plant. The portable light source was a hand held light and was adjusted to maximize viewing conditions. Moving the light source allowed the observer to control the lighting conditions, i.e., optimize the incident light angle and the effect of reflected light on the formulation residue, and minimize the reflecting light back to the observer. A light meter was used to set and verify the various light intensity levels.

The viewing distances for this study were dependent on the size of the equipment. In a commercial manufacturing facility, equipment sizes are larger and viewing distances are greater. Rather than define viewing distances for each piece of equipment, viewing distances were chosen at 5, 10, 15, and 20 feet to complement the pilot plant data.

The viewing angle is also restricted by the equipment size and configuration. Therefore, residues were viewed over a range of angles from 15° to 90°. The minimum angle resulted from a combination of comfortable viewing angle coupled with viewing distance. Intermediate viewing angles of 30° and 45° were evaluated in addition to perpendicular (90° to the observer) viewing.

Residue appearance varies from white, crystalline to gray. The standard preparation for residue spots involves pipetting 100 µl of sample solution or suspension onto the material coupon. This volume of methanol consistently supplies a circular residue spot of about 5 cm in diameter, which is approximately the 25 cm^2 area that is swabbed. As the sample concentrations decrease, the appearance of the residues is less likely to appear as a uniform residue and more likely to appear as a ring. The non-uniform or ring appearance of the residues at the VRL would be observed on equipment after cleaning. As residue levels increase, the VRL would fail a piece of equipment long before it became uniformly coated with residue. A uniformly visible residue would be so far above the VRL, it would indicate a completely ineffective cleaning procedure.

To minimize the effect of observer subjectivity, four subjects viewed all of the samples independently. Sample concentration levels in this study were spotted above and below the previously determined VRL to allow for increased distances and higher intensity light respectively. Therefore, the targeted spotting levels for the formulations were at the Acceptable Residue Limit (ARL) of the API, which is typically

Compound Information: Aprepitant in 1/1 ACN/Water								
Amt of Drug per Spot (ug/cm²)	**Observer A**	**Observer B**	**Observer C**	**Observer D**	**Observer A**	**Observer B**	**Observer C**	**Observer D**
	Visibility of Spots (1400Lux) Fluorescent Light				Visibility of Spots (1000Lux) Fluorescent Light			
74.4	Y	Y	Y	Y	Y	Y	Y	Y
40.1	Y	Y	Y	Y	Y	Y	Y	Y
14.2	Y	Y	Y	Y	Y	Y	Y	Y
12.0	Y	Y	Y	Y	Y	Y	Y	Y
7.44	Y	Y	Y	Y	Y	Y	Y	Y
5.90	Y	Y	Y	Y	Y	Y	Y	Y
2.98	Y	Y	Y	Y	Y	Y	Y	Y
1.45	Y	Y	Y	Y	Y	Y	Y	Y
0.00	N	N	N	N	N	N	N	N
	Visibility of Spots (800Lux) Fluorescent Light				Visibility of Spots (600Lux) Fluorescent Light			
74.4	Y	Y	Y	Y	Y	Y	Y	Y
40.1	Y	Y	Y	Y	Y	Y	Y	Y
14.2	Y	Y	Y	Y	Y	Y	Y	Y
12.0	Y	Y	Y	Y	Y	Y	Y	Y
7.44	Y	Y	Y	Y	Y	Y	Y	Y
5.90	Y	Y	Y	Y	Y	Y	Y	Y
2.98	Y	Y	Y	Y	Y	Y	Y	Y
1.45	Y	Y	Y	Y	Y	Y	Y	Y
0.00	N	N	N	N	N	N	N	N
	Visibility of Spots (400Lux) Fluorescent Light							
74.4	Y	Y	Y	Y				
40.1	Y	Y	Y	Y				
14.2	Y	Y	Y	Y				
12.0	Y	Y	Y	Y				
7.44	Y	Y	Y	Y				
5.90	Y	Y	Y	Y				
2.98	Y	Y	Y	Y				
1.45	Y	Y	Y	Y				
0.00	N	N	N	N				

Table A. Observer variability of visual cleanliness of aprepitant versus light intensity.

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		Visible Limit (ug/cm²) at Specified Illuminance				
API	**Product**	**400 Lux**	**600 Lux**	**800 Lux**	**1000 Lux**	**1400 Lux**
Indinavir Sulfate	Crixivan®	< 1.38	< 1.38	< 1.38	< 1.38	< 1.38
Aprepitant	Emend®	-----	1.45	1.45	1.45	1.45
Alendronate Sodium	Fosamax®	0.495	0.495	0.495	0.495	0.239
Rizatriptan Benzoate	Maxalt®	< 0.873	< 0.873	< 0.873	< 0.873	< 0.873
Finasteride	Proscar®	< 2.72	< 2.72	< 2.72	< 2.72	< 2.72
Montelukast Sodium	Singulair®	< 1.47	< 1.47	< 1.47	< 1.47	< 1.47
Enalapril Maleate	Vasotec®	< 0.65	< 0.65	< 0.65	< 0.65	< 0.65
Simvastatin	Zocor®	0.485	0.485	0.400	0.485	0.485
Compound A		0.552	0.552	0.552	0.552	0.552
Compound B		< 0.591	< 0.591	< 0.591	< 0.591	< 0.591
Compound C		0.666	0.666	0.666	0.666	0.666
Compound D		5.59	1.61	1.61	1.61	1.61
Compound E		5.85	1.85	1.85	1.85	1.85
Compound G		-	6.25	6.25	6.25	6.25
Compound H		1.75	1.75	1.75	1.75	1.10
Compound I		3.01	3.01	3.01	3.01	3.01
Compound J		-	5.43	0.930	0.930	0.930
Compound K		1.97	1.97	1.97	1.97	1.97
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Table B. Visible residue limits of Merck compounds versus light intensity.

4 µg/cm², the previously determined VRL**,** at the VRL + 25% and at the VRL - 25%.[9]

Experimental

Samples were prepared by dissolving or dispersing 25 mg of material into 25 ml of solvent resulting in a 1.0 mg/ml or 1000 µg/ml sample. Different volumes of the sample were spotted onto the stainless steel coupons along with a complementary volume of solvent so the total volume spotted was constant. A series of residues spotted for each sample along with a solvent blank typically resulted in spot concentrations from less than 0.2 to 4 µg/cm² or 5 to 100 µg/25 cm² swab.

The spots were dried under a stream of nitrogen to aid in drying and to prevent potential oxidation of the material. Even though the same volume of sample/solvent was spotted, different dried residue areas resulted as the liquid samples spread out over the coupon. The sample spread came from differences in the condition of the stainless steel coupons and from passing nitrogen over the samples during drying. The areas of the dried spots were measured to determine the Amount per Unit Area (µg/cm²) value for each spot of material.

The spots were viewed under controlled conditions. The light source was maintained in a stationary position directly above the samples. The observers were oriented such that they viewed the spots from the same three-dimensional location each time. Each observer wore a white lab coat to minimize variations caused by individual clothing colors. The observers viewed the coupons separately so as not to influence the responses of the other participants. The coupons were positioned for viewing, and the light intensity measured on the same spot on the samples - *Figures 1 and 2*.

Range of Residue Concentration Levels among Observers	Number of Compounds
0	10
1	32
2	8
3	5
4	4
5	1

Table C. Observer variability determining Visible Residue Limits.

Results and Discussion

Pilot Plant Study

Visible residue limits were established for Active Pharmaceutical Ingredients (APIs), commonly used excipients, and a number of formulations. Each visible limit was that concentration at which all observers positively identified a visible residue. The actual amount of material spotted in µg/cm² was a result of the amount of material weighed for the sample, the volume of solution/suspension spotted on the coupon, the subsequent area of the liquid on the coupon, and the resulting residue area. Each of the four observers viewed the spots and indicated whether or not they saw any visible residue. Examples of one of the API results are shown in Table A.

The only study condition varied for the pilot plant study was the light intensity. Fourman and Mullen determined a visible limit at approximately 4 µg/cm².[4] However, the light intensity and individual residues were not addressed. Jenkins and Vanderwielen observed various residues down to 1.0 µg/cm² with the aid of a light source.[5] One could logically expect the visible residue limit to decrease with increasing light intensity. Although there were changes in the detected visible residue limit, it should be noted that the changes were minor. Overall, the ability to detect VRLs was not significantly affected over the light intensity range - *Table B*.

The primary concern for the use of visible residue limits is

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VRL(μg/cm2)	APIs	Formulations	Excipients	Detergents	Total	%Total
< 1	54	50	45	8	157	68%
1 – 2	19	9	8	3	39	17%
2 – 3	10	2	4	1	17	7%
3 – 4	3	2	1	0	6	3%
> 4	6	0	5	0	11	5%
Total	92	63	63	12	230	100%

Table D. Visible Residue Limits (VRLs).

the training of the observer to inspect clean equipment. The more comprehensive the training, and the greater the experience level, the less variability encountered. Table C shows the range of variability of the first 60 detergents, excipients, APIs, and formulations tested. In 10 of the cases all four observers agreed on the visible residue limit. In more than 80% of the tests, there was some difference of opinion as to what was visibly clean. Most of these differences were minor, but there were several cases that could be cause for concern. As the observer experience level increased, the observer variability decreased, as did the VRL levels.

The safe application of VRLs depends on the difference between the VRL and the ARL. The greater the margin, the greater the safety factor when addressing the variability of the observer parameters. Of the 230 VRL determinations to date, 85% were below 2 μg/cm^2 and 95% were below the adulteration limit of 4 μg/cm^2 - *Table D*. The margins in the large majority of cases are wide enough to alleviate potential concern over variability of viewing parameters and observer determination.

Commercial Plant Study

As expected, the overall ability to visually detect formulation residue decreased with increased viewing distance - *Table E*. At 400 lux and at the minimum viewing angle, observers were able to detect the previously determined ARL, as well as the VRL for all tested formulations from five feet. Several of the formulation VRLs were not detected from 10 feet. From 15 feet, the observers were not able to see the majority of the VRLs and were not able to detect any of the VRLs consistently from 20 feet. With regard to the ARLs, the observers saw the majority of the formulation residues under these viewing conditions from 10 and 15 feet. From 20 feet, the observers saw less than half of the formulation ARLs.

The ability to detect visible residue also diminished with decreased ambient light - *Table F*. With ambient light down to 200 lux, VRLs were consistently detected from 15 feet and a 45° viewing angle. With ambient light at 100 lux, some VRLs were not detected at 15 feet and 45°. However, VRLs were consistently detected from 10 feet at 100 lux.

The ambient light source controlled the light intensity at the lower end of the range. The portable light source controlled the light intensity at the upper end of the range. The observer moved and adjusted the orientation of the portable light source to optimize individual viewing conditions within the constraints encountered in different manufacturing equip-

400 lux, 15°	5 feet				10 feet				15 feet				20 feet			
Product	75% VRL	VRL	125% VRL	ARL	75% VRL	VRL	125% VRL	ARL	75% VRL	VRL	125% VRL	ARL	75% VRL	VRL	125% VRL	ARL
Cozaar									1	1	2		4	4	3	2
Crixivan									2	2			3	3	2	1
Cuprimine					2	2	3	3	3	3	3	3	4	4	4	4
Demser					1	1	1		2	2	2	2	2	2	2	2
Diuril					2	1			4	4	1		4	4	2	
Emend									3	3	2		2	2	2	1
Formulation A									1	1	2	2	4	4	3	2
Formulation B									3	3	3	2	3	3	2	1
Formulation C											1		3	3	2	1
Formulation D									1	1			3	2	2	
Fosamax					2	1	1	1	2	2	3	3	4	3	3	2
Indocin													1	1		1
Maxalt									4	3	1		3	3	2	1
Pepcid							1		2	2	2		4	4	2	1
Proscar													3	2	2	
Singulair													2	2	1	
Syprine					4	4	4	4	4	4	4	4	4	4	4	4
Vasotec									2	2	1		4	4	2	
Zocor, 10											1		3	3	1	
Zocor, 20									2	2			3	3	2	1
Key: Blank box – Residue detected by all four observers. Numbered box – Residue not detected by indicated number (out of 4) of observers.																

Table E. Effect of viewing distance on Visual Residue Detection.

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15 ft, 45°	400 Lux				300 lux				200 lux				100 lux			
Product	75% VRL	VRL	125% VRL	ARL	75% VRL	VRL	125% VRL	ARL	75% VRL	VRL	125% VRL	ARL	75% VRL	VRL	125% VRL	ARL
Cozaar													4	4	1	
Crixivan													4	4	1	
Cuprimine			4	4	2	1	4	4	2	1	4	4	1	1	4	4
Demser					1								3	1	1	1
Diuril									1		1					
Emend	1		1										4	4	3	
Formulation A													1	1	1	
Formulation B													1	1	1	
Formulation C													1	1	2	
Formulation D													1	1	1	
Fosamax	4	2			1				1	1			2	2	2	
Indocin									1							
Maxalt													2	2	1	
Pepcid	1	1	1										1	1	1	
Proscar													1	1	1	
Singulair													1	1	1	
Syprine	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Vasotec	1	1											1	1	1	
Zocor, 10													1	1	1	
Zocor, 20													1	1	1	
Key: Blank box – Residue detected by all four observers. Numbered box – Residue not detected by indicated number (out of 4) of observers.																

Table F. Effect of light intensity on Visual Residue Detection.

ment; therefore, the maximum intensity of the portable light source decreased with distance.

In general, the use of the spotlight did not increase the observer's ability to detect formulation residue. The intensity of the spotlight overwhelmed the residue and/or the reflecting light from the spotlight hindered the observer's ability to detect the residue. There were several instances where the use of the spotlight enabled the observer to see a previously undetected spot. However, there were more instances where the observer did not detect a residue with the spotlight, but

400 lux, 15ft	90°				45°				30°				15°			
Product	75% VRL	VRL	125% VRL	ARL	75% VRL	VRL	125% VRL	ARL	75% VRL	VRL	125% VRL	ARL	75% VRL	VRL	125% VRL	ARL
Cozaar													1	1	2	
Crixivan									1	1			2	2		
Cuprimine	1		4	4			4	4	1	1	4	4	3	3	3	3
Demser													2	2	2	2
Diuril									1			1	4	4	1	
Emend	1		1		1		1		2	2	3		3	3	2	
Formulation A													1	1	2	2
Formulation B									3	3	2	1	3	3	3	2
Formulation C									2	2	3	1			1	
Formulation D													1	1		
Fosamax	3	1			4	2			2	2	2		2	2	3	3
Indocin																
Maxalt	1								3	3	3		4	3	1	
Pepcid	1	1			1	1	1		2	2	2		2	2	2	
Proscar																
Singulair																
Syprine	4	4	4	4	4	4	4	4	3	3	3	3	4	4	4	4
Vasotec			1		1	1			2	2	2	1	2	2	1	
Zocor, 10															1	
Zocor, 20									2	2	1	1	2	2		
Key: Blank box – Residue detected by all four observers. Numbered box – Residue not detected by indicated number (out of 4) of observers.																

Table G. Effect of Viewing Angle on Visual Residue Detection.

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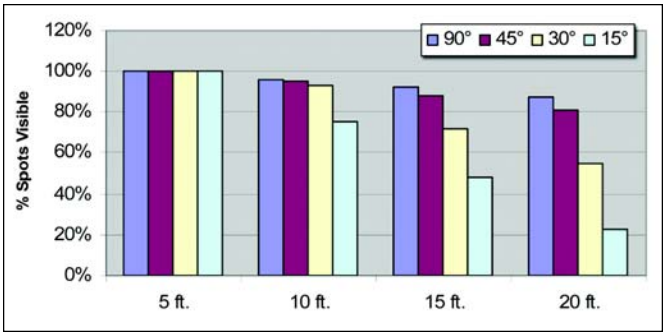

Figure 3. VRL detection versus distance and viewing angle.

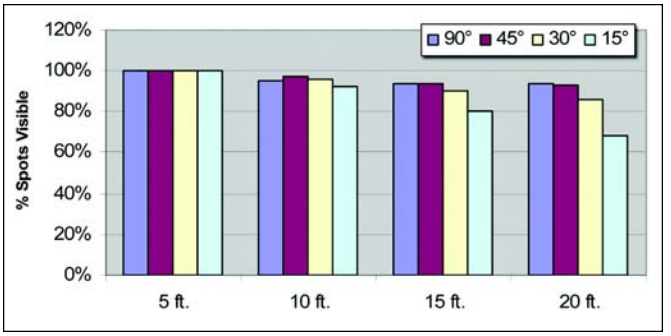

Figure 4. ARL detection versus distance and viewing angle.

was able to detect the same residue under ambient light. In practice, the effective use of a portable light source is an observer and situational issue.

The viewing angle of the observer to the residue was a critical parameter in the ability to detect the formulation residue. Under ambient light and at the minimum angle, about 15° (Table E), the observers did not detect the majority of the VRLs at 15 feet and only detected a few at 20 feet. When the viewing angle was increased to 30° (Table G), the observers detected more residue spots at both 15 and 20 feet, but not enough to make a significant difference compared to the 15° data. As the viewing angle was increased to 45° and 90°, the observers detected almost all of the VRLs at 15 feet (Table G) and detected the majority of the VRLs at 20 feet. The observers detected essentially all of the ARLs at 20 feet at viewing angles greater than 30°. When the position of the observer was varied with respect to the stainless steel background, observers detected all VRLs from 10 feet at a 45° coupon angle down to 100 lux.

Observer variability was a factor in determining the VRL[8] for API and formulation residues. The pool of observers were recruited based on job function, i.e., those performing VRLs, those cleaning the equipment, and those inspecting the equipment, but all had comparable visual acuity with or without corrective lenses. The observer's visual acuity had no obvious effects on the VRL data. For this study, each viewing parameter examined had an effect on the observer's ability to detect the formulation residues. Observer detection was dependent on the formulation residue level, observer viewing distance, light intensity, and viewing angle. Certain observers had trouble detecting several of the formulation residues. Observer variability increased with greater viewing distance. Viewing distance became a factor beyond 10 feet (Table E) and observer variability increased. This same trend was seen with the observer angle factor. At the minimum angle of 15° and at 30° (Table G), observer variability was comparable to the other parameters. However, at a viewing angle greater than 30°, the ability to detect residue increased significantly and observer variability decreased accordingly - *Figures 3 and 4*. Observer residue detection was comparable using the portable light source and ambient light at 400 lux (Figure 5) and was not a significant factor at decreasing light intensity levels until 100 lux, where detection of VRLs was problematic - *Figure 6*.

The parameters which influence the ability to detect visible residues were determined and viewing of residues can be controlled. Under defined viewing conditions, a trained observer will be able to visually detect formulation VRLs. The observer should be within 10 feet of the equipment surface. This minimizes the influence of the light intensity or viewing angle. Secondly, the observer should view the surface from multiple angles greater than 30°. This minimizes the possibility of the residue blending in with the background. Finally, the ambient light level should be at least 200 lux. Otherwise, a portable light source can be utilized.

Applications

Uses of VRLs by a Pilot Plant Facility

The use of VRLs has previously been described[8, 10] for the introduction of new compounds into a pilot plant. Before a new compound is manufactured in the pilot plant, a VRL is established for the API. After the initial batch is manufac-

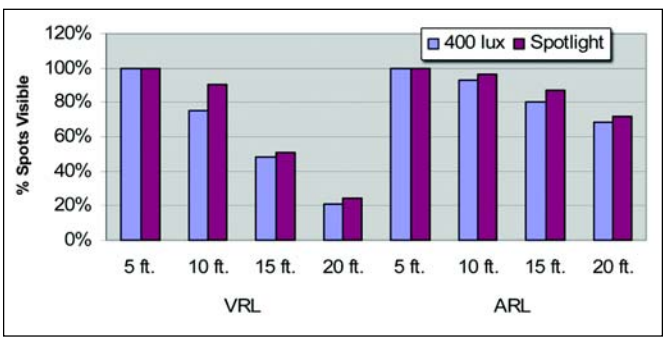

Figure 5. ARL and VRL detection at 400 lux and maximum light intensity.

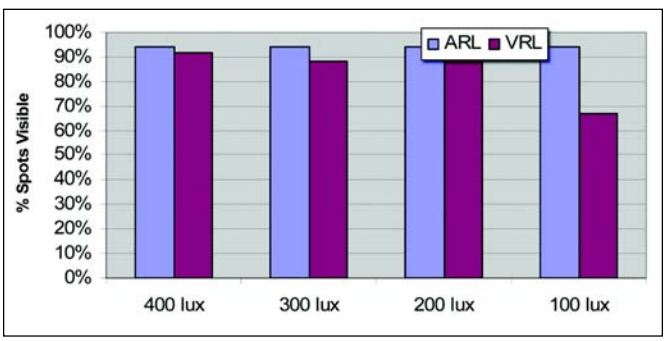

Figure 6. ARL and VRL detection versus decreasing light intensity.

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tured, the equipment is cleaned and visual inspection using the VRL confirms the current cleaning procedure is sufficient and that the new compound is not a new worst-case requiring further validation. This process has been successfully implemented without compromising product quality. This application along with its risk mitigation is shown in Table H.

VRLs also are used for periodic assessment of cleaning in the pilot plant. Monthly independent visual inspections using VRLs are conducted on several pieces of equipment to assure that routine cleaning removes all product residues. These inspections are in addition to routine visual inspections for cleanliness conducted after each use by the manufacturing technician. Over the course of the year, these independent periodic inspections check all of the different types of equipment in the pilot plant to generate a comprehensive review of ongoing cleaning effectiveness in the pilot plant.

Other uses of VRL in the pilot plant include technology transfer either to a contract or a manufacturing facility. Since cleaning procedures between facilities are different, VRLs would be a quick, simple verification of cleaning in place of analytical method transfer and testing. This strategy applies more to early development programs where the number of manufactured batches is limited and for compounds that are relatively non-toxic.

VRLs also can be used for the introduction of new equipment into the facility. VRLs would be used to ensure baseline cleanliness and demonstrate equivalency with respect to the cleaning efficacy of a previously validated procedure. Developing the cleaning procedure for new or modified equipment in conjunction with VRLs is an efficient way to get equipment on line.

The optimization of new cleaning procedures during development is a potential application for VRLs. Cleaning cycle times could be challenged with VRL determination as the acceptance criteria. A more immediate benefit would be realized with manual cleaning procedures. Personnel who clean the equipment could effectively determine optimal scrub times and rinse volumes with a visual limit.

The cleaning validation program of the pilot plant was based on qualitative visual inspection and swab sample testing.[6] A recent cleaning validation study[11] employed VRLs along with swab sample testing. The test compound had an ARL of 100 µg/swab. The VRL for the compound was 0.97 µg/cm^2 or 24.25 µg/swab. The 69 swab results ranged from 0 to 88 µg/swab, of which 10 were apparently above the VRL. The cleaned equipment passed both the swab testing and VRL inspection. However, the swab assay results were higher than expected based on the VRL data. An investigation concluded that the compound had reacted and formed an enantiomer with greater UV absorbance. The investigation demonstrated the value of establishing VRL data in conjunction with swab recoveries. However, in general, the visible limit is much lower than the swab limit, and swab results are typically well below the VRL, making any direct real-life comparison difficult. One could perform swab recoveries of the VRL spot residues to show correlation, but that only adds value if your ongoing swab samples are about that level.

Applying VRLs in a Manufacturing Facility

Several opportunities to apply VRL as a surrogate to surface sampling have been identified in manufacturing facilities using Good Manufacturing Practices (GMPs). Process controls and procedures also have been identified to mitigate the risks when applying VRL in a GMP facility. Given that VRL

VRL Application	Pilot Plant/Manufacturing	Process Risk	Risk Mitigation
New compound introduction	Pilot Plant	**Low** New worst-case	- VRL determination - Redundant inspection - Evaluate API physical properties
New compound introduction	Manufacturing	**Low** New worst-case	- Redundant inspection - Evaluate formulation physical properties and cleanability
Routine use inspection	Pilot Plant	**None**	- Already in place - Cleaning validation
Routine use inspection	Manufacturing	**None**	- Already in place - Cleaning validation
Periodic assessment	Pilot Plant	**Low** Carryover	- Redundant inspection - Periodic swab confirmation
Periodic assessment	Manufacturing	**Low** Carryover	- Redundant inspection - Periodic assessments trending performance based on visual inspections.
Technology transfer	Pilot Plant	**Low**	
New equipment introduction	Pilot Plant	**Low** Cleaning procedure doesn't work	- Redundant inspection - Evaluate versus current equipment
Campaign length extension	Manufacturing	**Low to None**	
Cleaning Procedure Optimization	Pilot Plant	**None**	- Surface sampling after optimization
Cleaning Procedure Optimization	Manufacturing	**None**	- Surface sampling and validation after optimization
Reduced Cleaning Documentation (Manual Cleaning, Equipment accessible to visual inspection)	Manufacturing	**Low to None**	- Data to demonstrate VRL < ARL - All cleaning parameters demonstrated during validation

Table H. VRL Application and risk assessment.

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determinations for drug product formulations have been established[8, 9] and the relative accessibility to visual inspections with this equipment, the scope of these applications would be primarily applicable to pharmaceutical manufacturing and primary packaging operations.

As with pilot plant facilities, VRL data may be used to develop new or optimize existing cleaning procedures. For manual cleaning procedures where the VRL is less than the ARL, the extent of routine documentation and cleaning records could be streamlined in a GMP facility. Once optimal scrub times and rinse volumes have been validated and incorporated into the cleaning procedure, visual cleanliness may be the only critical cleaning parameter that would require documentation on a routine basis. With VRL data, a check by a second person for visual cleanliness confirms performance and ensures that the level of residuals is below the acceptable residue level. This procedure may obviate the need to record actual cleaning parameter data (i.e., scrub times and rinse volumes) on a routine basis and reduce the volume of GMP documentation that must be maintained for marketed drug products.

VRL data and visual inspection may be applied to support the introduction of new products into existing validated product matrices. The use of product matrices or bracketing product residues to validate a "worst case" for multi-product equipment modules is a common practice in industry and supported by regulatory guidance.[3,12,13,14] Best practices include an evaluation of the different products and intermediates with respect to solubility and cleanability. Laboratory studies may be performed to directly compare the relative cleanability between the targeted compounds and products. Methodologies for rapid and inexpensive testing for cleanability have previously been reported.[15] The relative toxicity data for all compounds in the matrix also should be reviewed with the ARL set using the most potent compound. To validate the matrix, validation studies would challenge the cleaning on the worst-case compound to remove using an ARL calculated for the most potent compound in the matrix. As new products are introduced, toxicity and cleanability must be assessed as to whether the compound represents a new worst case. If not a new worst-case, the VRL of the new compound can be compared to the validated ARL. If the new compound is less than the ARL, visual inspection alone should be satisfactory for revalidation of the cleaning procedure for a new product.

The interval of use (manufacturing campaign) and the interval between end of use and cleaning are process parameters that must be validated. Theoretically, the more batches a piece of equipment processes, the greater the soil load, and the more difficult it is to clean. Hence, the need to challenge cleaning cycles after campaigns of different lengths. Nonetheless, some products' physical, chemical, and surface adhesion properties do not change over the campaign length. For manufacturing these products (dry processing), certain types of equipment do not allow residues to accumulate over time by design. This equipment is sloped for gravity removal of product, whereby the soil load (both the amount and nature of the soil) after one batch is comparable to the load after multiple batches within a campaign (i.e., "freely draining"). This can be verified by visual inspection on a routine basis. For stable products, manufactured in freely draining equipment, there should be low-to-no process risks with respect to extending a validated campaign length based on visual inspection. Routine inspections for visual cleanliness would mitigate any potential process risks with carryover of process residuals and confirm cleaning performance. The risks for bioburden proliferation are low due to the absence of water and moisture. This same rationale could be applied to extending validated times for the interval between the end of use and equipment cleaning.

Once a cleaning process is validated in a GMP manufacturing environment, the process should be monitored periodically to ensure consistent and robust performance. Independent visual inspections should be incorporated into the periodic assessment program to confirm that the cleaning processes remain in a state of control. A second person should check for visual cleanliness and the frequency of recleaning is an appropriate metric for assessing cleaning performance. This additional control helps to ensure robustness of the validated cleaning procedure. With an appropriate VRL program, visual inspection may be used rather than surface or rinsate testing to demonstrate continued consistent cleaning performance.

Conclusion

Visible Residue Limits (VRLs) have been evaluated for pilot plants and manufacturing facilities from a risk-assessment perspective. The VRL data, particularly when compared to the health-based cleaning limit for most compounds, makes VRL use a low risk approach to cleaning verification and validation. Opportunities for VRL implementation have been identified along with the acceptable mitigation of the associated risks.

Recent examination of the program, by the MHRA and review by FDA representatives have supported the use of a well defined VRL program.

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About the Authors

Richard Forsyth is an Associate Director with GMP quality at Merck & Co., Inc. He is responsible for internal and external facility audits as well as document audits for regulatory submissions. He has worked in Quality for two years and prior to that worked as an analytical chemist in Pharmaceutical R&D for 23 years. He has been involved with cleaning validation for more than 14 years. Forsyth has a broad range of GMP/GLP analytical experience including methods development and validation as well as formulation development and project management. Academic training includes an MS in chemistry and an MBA in management, both from St. Joseph's University in Philadelphia, Pennsylvania, USA. He can be contacted by telephone: +1-215-652-7462 or by e-mail: richard_forsyth@merck.com.

Merck & Co., Inc., WP53C-307, P.O. Box 4, West Point Pennsylvania 19486-0004, USA.

Mr. Jeffrey L. Hartman has more than 26 years of experience in the pharmaceutical industry, supporting API, pharmaceutical, and vaccine manufacturing. His expertise spans all areas of validation (cleaning, sterilization, process, sterile/aseptic operations, and computer/automation) regulatory science, facility start-up, and fermentation. Currently, he is a Validation Manager in Regulatory and Analytical Sciences, Merck & Co., Inc.; responsibilities include development of Merck Manufacturing Division guidelines/policies, quality system requirements, and support of validation activities worldwide. With more than 11 years of hands-on and consulting experience in cleaning validation, he is considered a leading Subject Matter Expert within Merck & Co., Inc.

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PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2008, Vol. 28 No. 3

GAMP 5 Quality Risk Management Approach

by Kevin C. Martin and Dr. Arthur (Randy) Perez

This article describes how the GAMP 5 quality risk management strategy offers a pragmatic approach to computer systems compliance.

Introduction

Background

In today's competitive and highly regulated environment in the life sciences industry, companies need to focus skilled resources where the risks are highest, thus minimizing risk to patients while maximizing resource utilization and efficiencies. To achieve this result, it is imperative to understand several critical issues. Companies must have a thorough understanding of their business processes and the Critical Quality Attributes (CQAs) of those processes. This knowledge along with appropriate risk management methods make it possible to identify potential areas that may fail, and to identify areas with acceptable risk or low risk that can be assigned a lower priority or effort for mitigation. It should be possible to reduce or eliminate unwarranted work at all risk levels, but especially on low risk areas, freeing critical resources to mitigate higher risks.

GAMP® 5 provides guidance in the application of risk management principles to the development of computer systems in GxP environments. It has become far less common than it was 10 years ago for life sciences firms to develop their own software. This leads to the generally positive consequence that most software is developed by companies whose continued viability is predicated on their delivery of good software. *GAMP 5* recognizes this fact, a point emphasized by the extensive appendix dedicated to supplier evaluation. It is appropriate to become involved in supplier software development and QA processes only if there is reason to doubt the integrity of these processes.

In this context, this article assumes that software and hardware are developed by the suppliers within a sound quality management system. Therefore, *GAMP 5* stresses consideration of risk to patients with the assumption that risks related to other business issues are covered by the supplier and the customer's standard system implementation processes.

The development of the *GAMP 5* risk management approach has its antecedents in the FMEA-based risk assessment tool published in *GAMP 4* in 2001. The approach matured in the 2005 ISPE *GAMP® Good Practice Guide: A Risk-Based Approach to Compliant Electronic Records and Signatures* with incorporation of aspects of ISO 14971 *Medical Devices – Application of Risk Management to Medical Devices.* The expansion of these concepts and the five step approach described in *GAMP 5* and this article are fully compatible with the approaches published in ICH Q9 *Quality Risk Management* (2005) and ASTM E2500 *Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment* (2007).

Determining the risks posed by a computerized system requires a common and shared understanding of the following:

- impact of the computerized system on patient safety, product quality, and data integrity
- supported business processes

Table A. GAMP 5 software categories.

Category	GAMP 4	GAMP 5
1	Operating system	**Infrastructure software** (OS, middleware, DB managers, etc.)
2	Firmware	No longer used — Firmware is no longer functionally distinguishable
3	Standard software	**Non-configured software** — Includes default configurable SW
4	Configurable software packages	**Configured software** — configured to satisfy business process
5	Custom software	Custom Software

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- Critical Quality Attributes (CQA) for systems that monitor or control Critical Process Parameters (CPP)
- user requirements
- regulatory requirements
- project approach (contracts, methods, timelines)
- system components and architecture
- system functions
- supplier capability
- the company's risk tolerance

The order in which the above is applied is not as important as ensuring that each area is addressed. However, it is imperative to understand several critical issues. First, it is essential to have a deep understanding of the relevant business processes and to understand CQAs of the processes.

It should be noted that the concept of CQAs is not new. They have been a part of Six Sigma, Mechanical Engineering and Software Engineering quality practices for years. CPPs are also a part of Six Sigma. Thus, these concepts are applicable in a far wider arena than in life science manufacturing; they are an aid to understanding the risks associated with any business process.

GAMP 5 relates how understanding of CQAs and CPPs can be applied to computerized systems in the life science industry with the intent of using them to the development of strategies for validation and verification. With such understanding, it is possible to identify potential areas of the automation that may fail to perform to expectation, and to identify those risk points that can be categorized as low or otherwise acceptable risk versus those that constitute unacceptable risk. It should be possible to reduce, or even eliminate, unwarranted work on low risk issues, freeing resources to be applied to more significant risks.

Although CQAs and CPPs are often identified and employed in relation to manufacturing systems, particularly process control or other computerized manufacturing processes, they are not frequently applied to non-manufacturing areas. However, there is no reason why the concepts should not be applied in other arenas; they can work just as well for a preclinical study as they do for a production line. The approach described in *GAMP 5* describes a framework that can be used in GMP and non-GMP areas equally effectively.

Analysis of CQAs can aid in the development of failure or defect scenarios in order to understand the downstream impact on the patient. With the scenarios identified, the ability to mitigate the risk or impact of the failure can be evaluated, presenting the potential to detect and intercept these faults before serious harm occurs. The ongoing monitoring of not only the process, but the effectiveness of mitigation for potential failure points, can help to reduce the likelihood that the potential failure may become a reality, and if it does, to recognize it early and contain or minimize its impact.

Historic Use of Risk-Based Approaches

Many companies have been using a "quasi-risk based" approach for years. The typical dilemma with validation of computerized systems has been deciding what to test, how much to test, and where should resources be applied to achieve optimum efficiency. Their validation processes often included risk assessments, but without a clear process for using the results of these assessments, they tended to be just another document in one of many binders of validation documentation. In lieu of a sound risk-based approach, these companies tended to err on the side of caution and conduct exhaustive and costly validation exercises.

Requirement documents have been used to help identify key process components, often times weighting them to assign to them a priority based on their relative importance. These types of tools have been used to determine where to focus resources and to identify the critical elements of our processes. Structured approaches such as root cause analysis and Kepner-Tragoe Analysis have been useful in the decision-making process. The critical areas would be documented and tested more than areas of lower criticality. Although the term risk was not necessarily used, the concern was about these critical processes operating properly and not failing. The problem resided in the fact that many viewed compliance as a black and white issue; zero risk meant compliance, and anything less was considered unacceptable.

More recently when 21 CFR Part 11 (August 1997) was first introduced, many formal company assessments included a 'risk filter' where the importance of the electronic record (or signature) was assigned a criticality factor. This was necessary as a part of "triage," deciding what systems needed remediation first. The higher the criticality, the more emphasis would be placed on ensuring that the integrity of the record was maintained. This was done not only for business reasons, but to assure product quality and subsequently patient safety.

Evolution of the Definition and Understanding of Risk

Risk management techniques have been in use for decades, early versions having their genesis in the 1940s. In the 1950s, military and aerospace industries began to apply risk approaches in the form of numerous MIL-STDs. The 1960s saw the creation of reliability engineering approaches (e.g., FMECA and HACCP). Certainly, the surge in the software development and technology industries drove the development of standards, in part impelled by the Computer Security Act of 1987 and the Information Technology Management Reform Act of 1996. NIST 800-30 Risk Management Guide for Information Technology Systems is one example. ISO-13485 also was accepted as a risk management standard throughout the product life cycle. The ANSI/AAMI/ISO 14971:2000 was published and applied to risk management of medical devices and replaced both ISO 13485 and EN 1441 (European standard) as the risk standard to be used for compliance in the medical device directives. Other industry standards organizations also contributed (e.g. IEEE, IEC, ISO, SEI, PMI).

The publication of ICH Q9 "Quality Risk Management" in 2005 is having a significant impact on our industry. The FDA, as well as other regulatory bodies, is embracing the Q9

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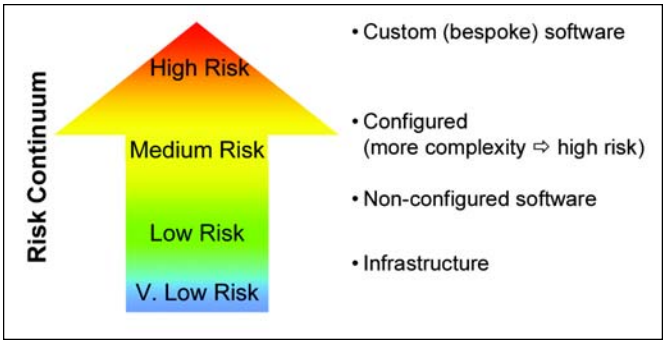

Figure 1. Risk continuum.

concepts. In general, Q9 provides high level guidance regarding:

- hazard identification
- estimating and evaluating risks
- controlling risks
- monitoring the effectiveness of the controls
- documenting the process used for risk management

The Q9 Introduction defines *risk* as the combination of the *probability* of occurrence of *harm* and the *severity* of that harm. It acknowledges the difficulty of achieving consensus or agreement on a risk management approach because of the diversity of the stakeholders. Therefore, with respect "to pharmaceuticals, although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality should be considered of prime importance."[1]

The GAMP Categories

The two primary principles of quality risk management are:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately be linked to the protection of the patient.
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk associated with the process.

One aspect of risk that can be leveraged with respect to computerized systems is the general trend that increased complexity of software implies higher risk for failure due to factors like buggy code, incorrect configuration, or improper implementation. Another unique factor for software is based on ubiquity; for some types of software (e.g., operating systems and database managers), there are so many copies on the market that it is a near-certainty that new faults will not compromise the applications running on them.

The GAMP categories enable a high level evaluation of risk based on the complexity of software or hardware in combination with general trends of reliability based on ubiquity.

When initially introduced, there were five GAMP categories - *Table A*. Since that time technologies have advanced and necessitated a change, which is being introduced in *GAMP 5*.

- The previous Category 1 (Operating Systems) is expanded to include Infrastructure Software and now also includes such layered software components as database managers, middleware, and ladder logic interpreters. Also included are tools used to manage the infrastructure, such as network performance monitors, batch scheduling tools, etc. This class is considered to be low risk due to two primary factors. First, infrastructure software is so ubiquitous that it is extremely unlikely that any unknown faults will exist. Second, this software is challenged indirectly in all other testing activities. While proper function of IT infrastructure may well be critical to satisfying a CQA, infrastructure will almost always have an extremely low probability of failure. Applications built on top of this software may fail, but it will seldom be attributable to failure of infrastructure software.

- Category 2 (Firmware) is no longer a separate category since modern firmware can be so sophisticated that there is no longer any justification for differentiation. Firmware can fit into any of the categories depending on the nature of the embedded software.

- Category 3 (Standard Software) has been renamed Non-Configured Software and includes many examples of firmware. Non-Configured in this sense refers to configuration to meet the needs of a business process; run-time parameters can still be configured. Off-the-shelf software has grown in sophistication to the point where some examples are configurable to meet the business process, and hence

Figure 2. Five step risk management approach. (Source: *GAMP® 5, A Risk-Based Approach to Compliant GxP Computerized Systems*,[8] used with permission from ISPE)

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could be considered Category 4. A simplified approach (Category 3) is allowed; however, a user can choose not to configure a simple configurable product and applies the default configuration.

- Categories 4 (Configured Software) and 5 (Custom or Bespoke Software) remain essentially unchanged with the exception that supplier assessments are suggested (i.e., discretionary), depending on the overall criticality of the system, as opposed to requiring supplier audits for all systems within the category.

The GAMP 5 software categories represent a broad indicator of likelihood of software failure. They can be a factor in planning test rigor – but not the only one. Large systems often comprise components of several categories; therefore, each category can help assess overall risk/impact of the components. The complexity of the components also can be useful in evaluating rigor needed for supplier assessment. Risk is a continuum and because the GAMP 5 categories are generalizations, they are not absolute, but can be useful as a tool used in the overall risk process - *Figure 1*. Other significant factors related to the risk of software includes the quality processes of the supplier (it is certainly possible to make bad infrastructure software), the integrity of the implementation process, and of course the use to which the software is put.

The key to maximizing the usefulness of the GAMP categories is to fully realize that they represent general conclusions about wide classes of software, and that they should only be one of the factors considered when planning a validation/verification strategy for a system.

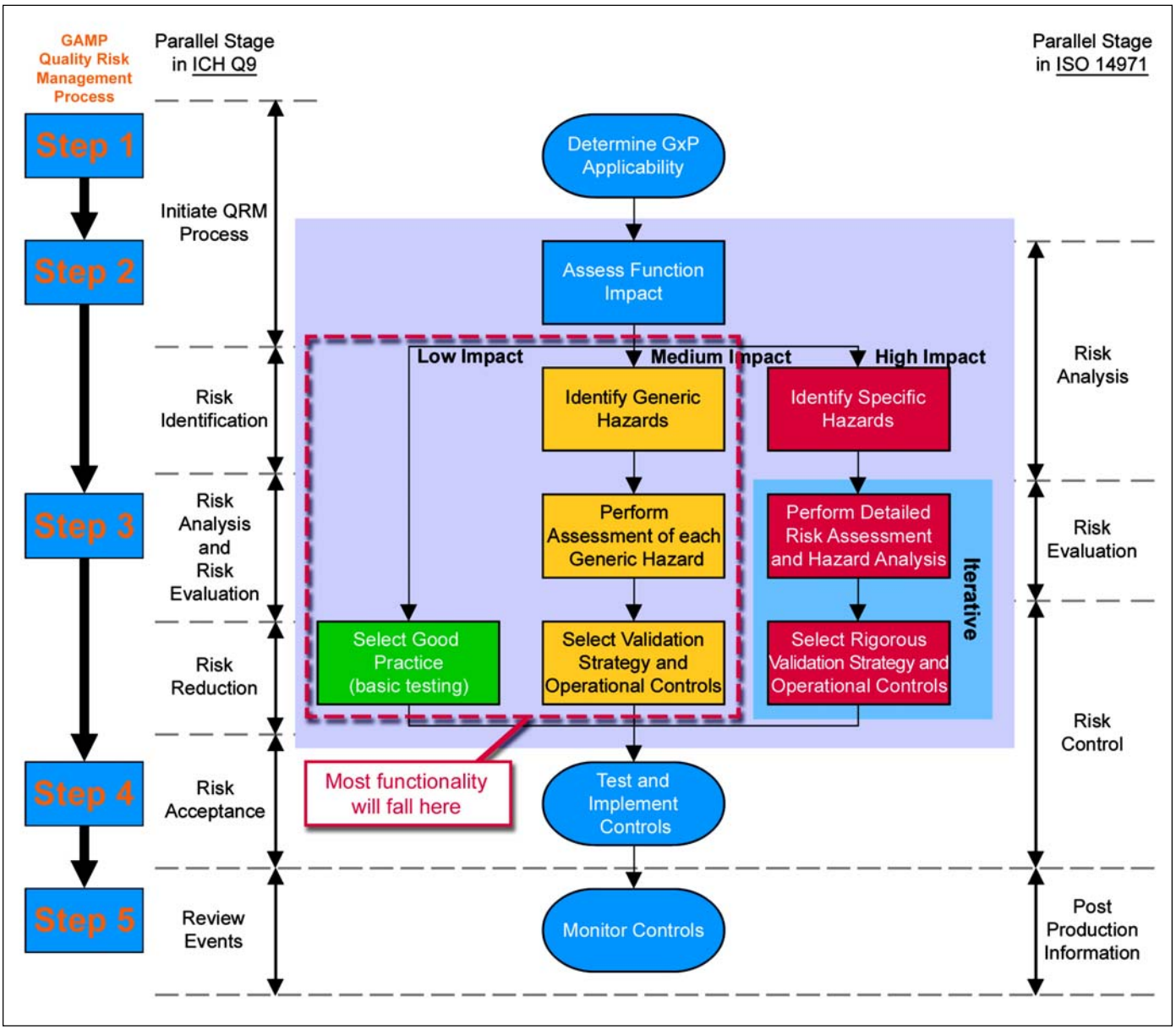

Figure 3. Risk assessment effort scaled according to function impact. (Source: *GAMP® 5, A Risk-Based Approach to Compliant GxP Computerized Systems*,[8] used with permission from ISPE)

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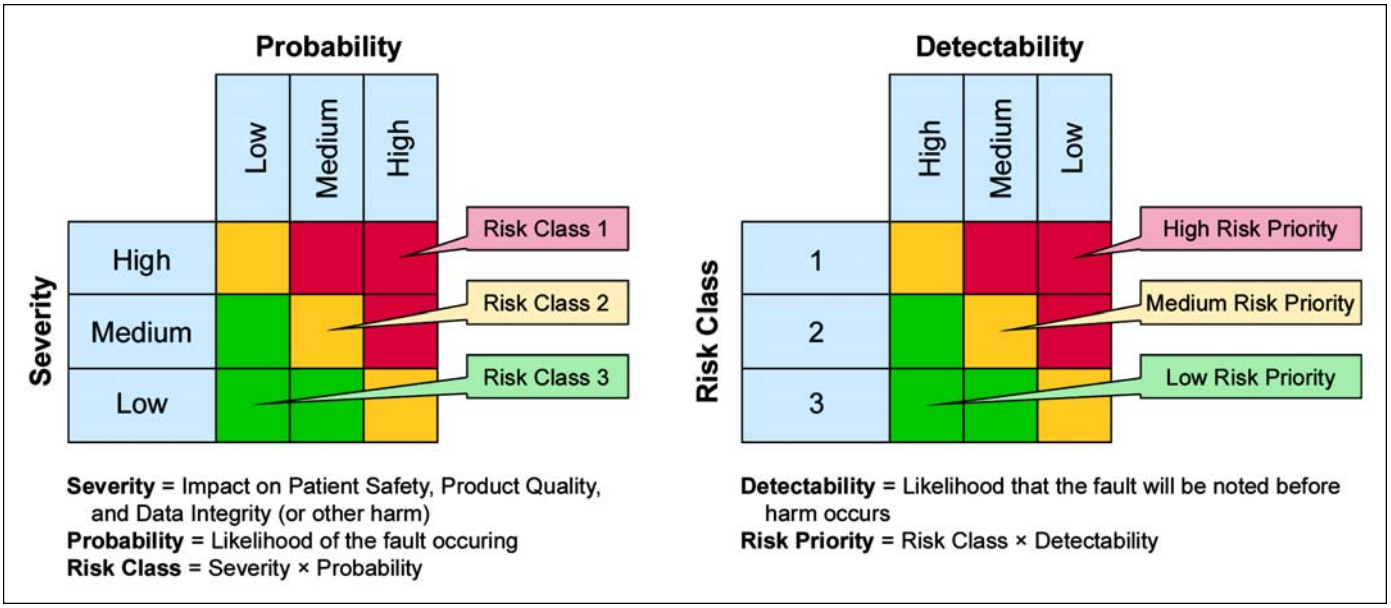

Figure 4. GAMP 5 risk assessment method. (Source: *GAMP® 5, A Risk-Based Approach to Compliant GxP Computerized Systems*,[8] used with permission from ISPE)

Five Step Approach to Risk Management for Computerized Systems

Guiding Principles

GAMP 5 is a science-based approach to understanding and managing risk for computerized systems. It is focused on a 'top-down' approach that looks at *processes* before *systems* or *functions*. Determining the impact to patient health for automated systems is not possible without a thorough understanding of the underlying business processes. Further, the risk associated with a computerized system cannot be greater than the risk associated with the processes it supports. The approach is forward looking in that it is compatible with new initiatives, such as the forthcoming ISPE Baseline® Guide that will present an alternative approach, and aligns well with the recently published ASTM 2500-07 standard. Although there are many existing standards available, ISO 14971 and particularly ICH Q9 were selected as the foundation for the *GAMP 5* Quality Risk Management (QRM) approach.

The central tenet of the *GAMP 5* approach is to define acceptable practices and apply stronger measures only where warranted. The approach should be simple in that an assessment result should indicate where additional controls are needed based on the relative risk. An added benefit by keeping the approach simple is that there should be only minimal impact when a company transitions from old compliance programs to new ones.

Process Description

It should be noted that organizations may have already established processes for risk management. While GAMP 5 provides one suggested approach, it does not intend that companies discard their current practices, rather that they continue to be used as appropriate within the overall quality risk management framework consistent with ICH Q9.

The *GAMP 5* Quality Risk Management approach is based on a simple five step process - *Figure 2*, where the emphasis is on constantly narrowing the focus to the point where rigorous testing and additional controls are only applied where the risk warrants.

Step 1 – Initial Assessment

An initial assessment should be performed based on an understanding of the business processes. The understanding can be derived from user requirements, design specifications, operating procedures, regulatory requirements, and known functional areas. The assessment should include a decision on whether the system is GxP regulated and include an overall assessment of the system impact. Further, it should include an evaluation of the process for impact to patient health, as many of the later steps in this process are dependent on this for the purpose of determining the scale of effort.

Since this step is geared toward understanding the business process, it is critical to ensure user involvement in the assessment and their acceptance of the outcome.

Step 2 – Identify Functions with Impact on Patient Safety, Product Quality, and Data Integrity

Building upon the information obtained in Step 1, the specific functions that have impact on patient safety, product quality, and data integrity can be identified and addressed. It must be remembered that no function can be assessed as having higher risk or impact than the process itself. The functions are typically listed in tabular form to be used in Step 3. Similarly to Step 1, user involvement is important to ensure that the impact of a system function on the business process (and ultimately on patients) is understood.

Step 3 – Perform Functional Risk Assessments

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and Identify Controls

The functions identified in the previous step can now be analyzed by considering possible hazards and what controls may be needed to minimize potential harm. A company's risk tolerance is also a factor to be considered when selecting possible controls. The rigor of the risk analysis can be adjusted based on the impact of the function as determined in Step 2 - *Figure 3*. For low impact functions, no further assessment of failure scenarios is warranted. For medium impact systems, generic hazards are identified and assessed, for example, a generic scenario for power loss might be assessed for a data acquisition system. For high impact functions in this system, specific hazards are analyzed, e.g., power problems that might include simple power failure, power failure with a voltage spike (lightning), or a voltage drop (brownout). For high impact functions, it is helpful (and recommended) to establish a strong link between the final user and the computer system supplier, whose deep knowledge of the system itself can ensure a correct functional risk assessment and suitable controls identification.

To execute these assessments, *GAMP 5* retains the simple FMEA-derived risk assessment process described in *GAMP 4 - Figure 4*. After identifying potential hazards, severity is plotted against the probability of occurrence to obtain the Risk Class. The Risk Class is then plotted against detectability to obtain the Risk Priority. Conveniently, this assessment lends readily itself to a semi-automated documentation approach using a spreadsheet.

As Figure 3 also illustrates, this process is aligned with the defined process steps of ICH Q9 and ISO 14971.

Step 4 – Implement and Verify Appropriate Testing and Controls

Once the severity and risk are understood, the appropriate level of challenge testing can be selected. Figure 5 illustrates the concept of planning testing and selecting controls based on assessed risk and impact. In general, functions with low risk will require little or no functional testing to meet compliance needs; testing of such functions to meet normal business expectation as defined in the development methodology is adequate. For medium impact functions, it is appropriate to consider generic failure modes, i.e., what will happen if the function fails. In the example mentioned above, this might entail a single test case for power loss. For high impact systems, the relevant specific risk scenarios should be tested. In the example above of power problems, test cases might be executed for each of the three cases noted (power loss, power loss accompanied by a voltage spike, and brownout conditions).

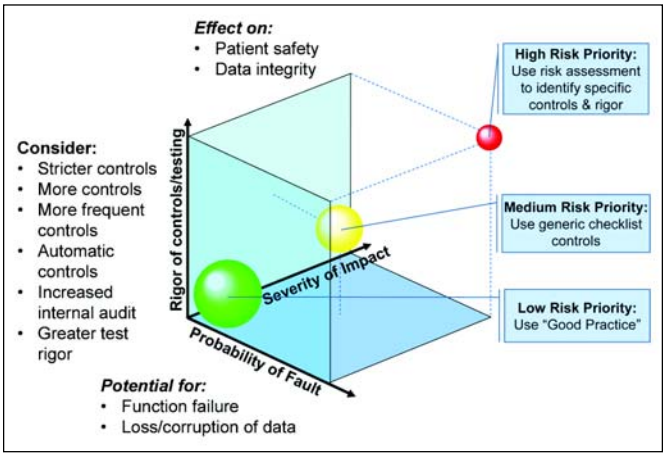

Figure 5. Relationship of risk, severity, and control.

Based in part on the outcome of testing, controls can be applied. If testing has shown that the system is robust enough, controls may not be warranted or may perhaps be emplaced to establish redundancy for high risk functions.

If testing reveals some gaps that need remediation, the selected controls should be commensurate with the assessed risk. Typically, low risk elements will require only "Good IT Practices." This entails the processes and practices that would normally be applied to a well-controlled IT operation for any company. Medium impact elements will require somewhat stricter controls, and high impact elements will require even greater controls. Controls should be traceable to the identified risks and need to be verified that they are effective in producing the intended risk reduction. An assessment of residual risk, i.e., the risk status following the application of the selected controls, should be performed for functions initially determined to be high risk.

Step 5 – Review Risks and Monitor Controls

Once the controls are implemented, they need to be monitored. The implementation of the controls may reduce the level of effort for many current activities, such as audits, assessments, documentation, testing, and even the degree of quality unit involvement. By communicating the resultant impact of implementing these controls, other benefits may be realized such as:

- benchmarking against standards
- measuring the amount of value added to the process
- determining the cost, regulatory, and legal impact
- developing a Risk-Based ROI model

After the controls are selected, the residual risk needs to be evaluated to ascertain if the controls are adequate and if the level of risk is acceptable. If the controls are too stringent, a more efficient approach may possibly be suggested.

Periodic evaluation after the system is operational will lead to improvement of the processes, controls, and overall risk strategy. The review should

- consider whether previously unrecognized risks are present
- determine if previously identified hazards are still present (and to what level)
- ascertain if the estimated risk associated with a hazard is no longer acceptable
- evaluate whether all existing controls are still necessary

The level of risk will determine the frequency of review and when in the life cycle the review should occur although review

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should always be part of the change control process. As in any aspect of risk management, the activity should ideally be a team-based exercise.

Summary

The GAMP 5 QRM strategy offers a pragmatic approach to computer systems compliance. It avoids reliance on a single standard that can be excessive and/or inadequate, and is consistent with ICH Q9 and has incorporated some elements from ISO-14971. It is a framework that is flexible and scalable and assists with the identification and application of appropriate controls where they are needed.

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Acknowledgement

We would like to express my gratitude to the members of the GAMP Risk Management SIG and GAMP Steering Committee who reviewed and provided substantive comments, and in particular, Steve Coates whose leadership was a driving force for this article.

About the Authors

Kevin C. Martin is Vice President of Regulatory Compliance Business Development for CimQuest-Vantage LLC, and has more than 30 years of pharmaceutical industry experience that includes management positions at Wyeth and McNeil Pharmaceutical. He is considered a subject matter expert for computer systems compliance within the QA, IT/IM, Manufacturing/Operations, Clinical, and R&D environments. He is a former member of the PhRMA Computer Systems Validation Committee, a former chair of the ISPE DVC CSV Sub-Committee, was a Core Team member for the PDA Part 11 Task Group, is a member of the GAMP Americas Steering Committee and is the GAMP Americas Sponsor to the Risk Management SIG. Martin holds a BS in chemistry from Delaware Valley College of Science and Agriculture and a Master of Engineering in manufacturing systems from Penn State University. He can be contacted by telephone: +1-215-260-6327 or by e-mail: kevin.martin@cimquest.com.

CimQuest-Vantage LLC, 35 E. Uwchlan Ave., Suite 330, Exton, Pennsylvania 19341, USA.

Dr. Arthur (Randy) Perez, Executive Expert, IT Quality Assurance for Novartis Pharmaceuticals, has served on the ISPE International Board of Directors since 2005. His responsibilities at Novartis include a wide range of IT Compliance issues, such as GxP, Sarbanes-Oxley, and data privacy. He serves on several global Novartis teams dealing with computer systems compliance issues, and has authored many of the firm's global GxP compliance policies. During his 25-year tenure at Novartis, he has developed a broad range of experience, working as a chemistry group leader in process research, managing a chemical manufacturing process validation program, and running a QA validation group for pharmaceutical operations. He was a member of the PhRMA Computer Systems Validation Committee and was instrumental in the formation of GAMP Americas when that group started in 2000. He initiated and led the Global Information Systems SIG, which wrote a GAMP® Good Practice Guide that was published in 2005. In 2002, he was elected Chairman of GAMP Americas and became a member of the global GAMP Council. Perez has been a speaker and a course leader at numerous ISPE Continuing Education seminars in the US and Europe, and has been published in industry journals and textbooks. He can be contacted by telephone: +1-862-778-3509 or by e-mail: arthur.perez@novartis.com.

Novartis Pharmaceuticals, One Health Plaza, East Hanover, New Jersey 07936, USA.

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PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2008, Vol. 28 No. 3

Creating Quality by Design/Process Analytical Technology (QbD/PAT) Management Awareness

by Christian Woelbeling and the Regional PAT COP from ISPE DACH Affiliate

This article summarizes the first four chapters of the PAT awareness document created by the PAT COP and explains how QbD/PAT management awareness can be created.

ISPE Germany/Austria/Switzerland Affiliate
ENGINEERING PHARMACEUTICAL INNOVATION

Introduction

The Communities of Practice (COPs) are one of the most important tools in ISPE for improving communication and networking within interest groups. In addition to globally acting COPs, regional COPs are in place to allow regional ISPE members, like the ones in the Germany (D), Austria (A) and Switzerland (CH) Affiliate (DACH) to exchange technical information and meet on a local level.

In 2005, the ISPE DACH Affiliate board members decided to establish a Process Analytical Technology (PAT) Special Interest Group (SIG). The focus of this group is not the "classical" PAT, but rather the new "science and risk-based approach" that is supported by ICH topics Q8, Q9, and Q10. Q8 and Q9 reached Step 3 (public consultation) of the ICH process in November 2005 and, hence, this SIG work, which began on 23 May 2005 with a one-day meeting, was conducted in parallel with finalization of these ICH guidelines. The feedback from 48 delegates revealed such strong interest in PAT issues that a questionnaire was distributed to the ISPE DACH members to evaluate the level of knowledge around the PAT initiative arising from, for example, the guidance document "PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance" published by the FDA in September 2004. More than 50 questionnaires were returned and the results revealed that there was a real lack of information and a great deal of interest in obtaining more information and exchanging experience within the context of an informal PAT SIG.

To date, the group has held eight successful meetings, including many lively discussions and educational presentations. In autumn 2006, during the ISPE Annual Meeting, the SIG turned into a regional COP, integrated into the global ISPE PAT COP. The first meetings served to find a common understanding of the new PAT initiative coming up with the risk-based and Quality by Design (QbD) approach. Two issues were identified as the biggest hurdles for PAT projects – a lack of management awareness and the financial justification to launch PAT projects.

Thus, the group decided to write a document entitled "Creating QbD/PAT Management Awareness."

Figure 1. 28 people joined the PAT COP workshop meeting in Frankfurt in March 2006.

Figure 2. Lively discussions in four Work Groups provided good results.

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Authority View	Commercial Management View
More pharmaceuticals	• Time to market • More innovation
with higher quality	• Reduced documentation • Optimized communication between authorities and industry • Guaranteed quality level ("unit-to-unit")
at lower cost	• Decreasing cost of production by improved productivity
	Further: Competitive advantage Image improvement Existing data and resources can typically be used

Table A. Authority View and Commercial Management View – the goals are the same!

This document and the activities of the local PAT COP also are intended to support the new ISPE Product Quality Lifecycle Implementation (PQLI) approach and to present and communicate this holistic strategy revealing the benefits coming from it.

In six main chapters, the document covers the following topics:

- Management Summary (Chapter 1)
- Why PAT – Drivers and Benefits (Chapter 2)
- Implication of PAT – Organization and Process (Chapter 3)
- Project Approach and Case Studies (Chapter 4)
- Structured Catalog of Standardized Questions with Benchmarking (Chapter 5)
- Case Studies – Completed Questionnaries (Chapter 6)

The various PAT awareness chapters were written as a group during five two-day face-to-face meetings. Through social events that fostered the exchange of knowledge, experience, and ideas, a real local networking community was formed.

This article summarizes the first four chapters of the PAT awareness document created by the PAT COP and explains how QbD/PAT management awareness can be created. Based on the results of their work sessions, the COP intends to present the PAT benefits to the top management of pharmaceutical companies to encourage investment in PAT-based projects in the future. The practicability of this approach has already been proven in one session held with a German pharmaceutical company.

Chapter 1: Management Summary

Currently, innovation in the pharmaceutical industry is limited due to post approval regulatory aspects (regulations and timings of approval) inhibiting the introduction of new and state-of-the-art technologies in validated processes.

Such processes are often fixed and finalized during clinical trials already. Process parameters and quality attributes are part of the registration file (license). Most variations require defined change control procedures. Therefore, post approval changes involve a great deal of effort such as registration activities and in some cases additional clinical trials.

Validated processes are by current definition inflexible and make process optimization measures or changes in feedstock by suppliers difficult. For example, variation in bio-feed stocks are difficult to handle under GMP conditions due to regional and seasonal variations. During the product lifecycle, process innovations to improve product quality continuously are related to high costs when changing the registration file with the authorities.

To reduce this effort in the different areas of the pharmaceutical industry, the FDA recommends in their PAT Guidance that quality is built into processes and products, a paradigm shift from the earlier practice of final product quality testing. ICH Q8 finalized in November 2005 suggests that if a higher degree of understanding is demonstrated that more flexible regulatory approaches could be proposed.

In order to build quality into processes and products, it is recommended that principles and tools such as QbD/PAT are used in an innovative way of thinking in developing and manufacturing pharmaceuticals. Pharmaceutical manufacturers have the opportunity to implement innovative and state-of-the-art technologies to improve production systems and achieve a sustainable cost reduction. QbD/PAT ensures consistently high level of product quality on the basis of a high level of process understanding with potentially flexible manufacturing processes. Thorough process understanding in combination with a well defined design space allows for much more flexible process control strategies (e.g., feed forward/backward loops) even if input parameters vary. Also, regulatory authorities may not consider variability of the operating conditions within predefined limits as changes - and thus provide what is called design space. Such a predefined degree of flexibility is a clear advantage compared to the current situation.

If the industry is aware of regulatory flexibility, companies can actively redefine their strategies by applying QbD/PAT principles. A better process understanding leads to more reproducible product quality and process robustness at a lower cost, thus improving competitiveness.

As can be seen in Table A, the authority view corresponds to the commercial management view, and the common goals can be reached by using QbD/PAT, an innovative way of thinking in manufacturing pharmaceuticals.

Chapter 2: Drivers and Benefits Justifying the PAT Approach

The goal of the PAT-oriented approach is to continue to ensure patient health by the availability of safe, effective, and affordable medicines.

This section summarizes and comments on PAT drivers and benefits from the perspective of regulatory authorities and the pharmaceutical industry to help decision makers with the interpretation and implementation of PAT strategies, processes, and tools in their organizations.

Regulatory Drivers

- assurance of affordable, safe, and effective drugs for all citizens

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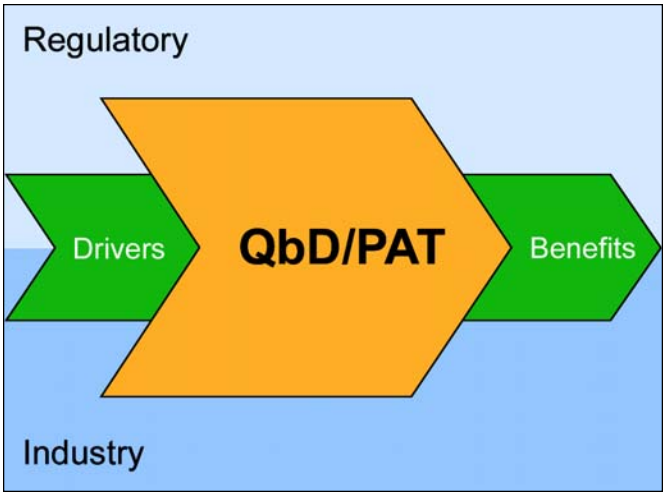

Figure 3. The QbD/PAT approach provides sufficient drivers and benefits for justifying successful projects.

- ensuring a high quality of drugs
- facilitating manufacturing process innovations

Only efficient research of new drugs, optimized processes, and dedicated quality control procedures will provide, in the future, affordable, safe, and effective drugs for all. The implementation of PAT principles and tools enables efficient manufacturing, while maintaining today's stringent quality standards.

Drug quality depends more on best development, production, storage, and distribution strategies than on expanded quality testing. With PAT, there will be a shift from lab-based end-product quality testing to better formulation and process design leading potentially to more in-line, on-line, or at-line testing.

Innovation transfer to routine production ensuring "state-of-the-art" manufacturing processes should be accelerated by regulatory authorities.

Potentially there should be fewer post approval regulatory submissions supporting process improvements.

Regulatory and Industry Benefits

- time to approval
- improved process understanding
- reduced inspection frequency

Time to market means in a first step "time to approval." Regulatory authorities are committed to reducing time for administration of Chemistry, Manufacturing, and Controls (CMC)/dossiers for new drugs as well as for submission changes of approved drugs. The key to reaching this goal is the appropriate presentation in the dossier of increasing complexity.

Improved process understanding helps both industry and authority with running, controlling, and monitoring processes on a well assessed science-and risk-based level. Process understanding is the basis for process control and assured end product quality. Finally, time and frequency for extended audits or inspections can be reduced if the process understanding meets the desired level. Up to now, this could not be detected in the available case studies.

Additional Industry Drivers

- reduced manufacturing costs
- more flexible manufacturing processes
- real-time release

PAT efforts could generate competitive advantages (i.e., a better corporate image, increased quality, and efficient management of risks). The costs of manufacturing or QA could be decreased by increasing productivity and greater availability of production equipment. Moreover, PAT offers the opportunity for interdisciplinary communication and for bridging the gap between the R&D, Manufacturing, QA, QC, and IT departments.

Manufacturing processes could become safer and more flexible under PAT. A defined design space (Quality by Design approach) for production processes offers flexibility for raw materials used, APIs, and even process controls. Because the influence of raw material variations is well known, the process control strategy allows adaptation to the variability of the raw material quality attributes. Process understanding results in an appropriate management of variability and improved operational efficiency (e.g., "Lean Manufacturing," "Right First Time" strategies). This leads to safer processes because the control strategies are optimized both from a pharmaceutical manufacturing and an operator point of view. Real-time release could help to reduce the time in warehouses of raw materials, final and intermediate products, or bulk (work in progress). PAT projects may start in single unit operations or could cover the whole production site. Incremental deployment is also enabled. In summary PAT should lead to a more efficient and reproducible supply chain.

Improved communication between the industry and the regulatory authorities is provided by the Regulatory Authorities' PAT teams ("pre-approval" activities).

Industry Benefits

- use of "state-of-the-art" technologies in manufacturing
- guaranteed quality level ("unit-to-unit")
- reduced documentation
- risk mitigation
- real-time data acquisition and integration
- knowledge management

The implementation of "state-of-the-art" and innovative production and control technology is encouraged. Knowledge transfer from other industries (e.g., IT, food, automotive, electronics) is reasonable and useful. A reduced transfer time from development to production by using PAT tools seems quite possible.

Reduced personnel placement, less Out-of-Specification (OOS) batches, reduced lead time, cleaning, set-up, or maintenance time, will lead to an increased Return on Investment

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(ROI). In the end, more efficient production processes will be obtained and yield will be increased.

The use of PAT tools can reduce documentation efforts, e.g., by modified validation approaches. Risk-based manufacturing could reduce frequency of audits.

Early and frequent feedback from the regulatory authority, PAT teams, and expanded communication within the context of pre-approval activities is mandatory for successful PAT projects.

PAT has the potential for drug quality improvements. Increased production safety and process robustness are created by an enhanced process understanding within all departments; including QA, QC, R&D, and Manufacturing. Risk mitigation by efficient risk management and the appropriate control of critical quality and process parameters will be the result of an adequate implementation of PAT tools.

Greater automation of processes helps to assess and control critical process parameters within the design space. A shift from classical lab-based testing to on-line, in-line, and at-line testing leads to fast, reliable, and real-time information about product quality within manufacturing processes. Data should be available, auditable, and easy to interpret at all times. Enhanced process information will be created by structured data management. The process know-how can be documented by process fingerprints, statistical methodology, or a total process approach (e.g., upstream, downstream, tablet production). Knowledge management is the basis for a better process understanding and process transfer from development to manufacturing.

Chapter 3: PAT Implications on Organization and Process

The PAT approach is influencing the organizational structures and the business processes as detailed below.

A) Implications on the Organization

Implications on Personnel

- Demand on qualification and/or skills of employees may change:
  - PAT may have an impact on qualification profiles in respect to scientific data analysis, statistics, process control, etc. Similar to implementing Six Sigma, implementing a PAT program may require dedicated training on methods and tools, including project management and statistics. (Probably at all levels of the company comparable with the Six Sigma training structure – master black belts, black belts, green belts, white belts?)

- Structural change within the organization:
  - There may be a need for the implementation of a new department or restructuring of departments to deal with the new demands.
  - Interactions and collaborations between departments and functions may need to be increased (e.g., quality, regulatory, development, commercial production).
  - Contact with regulatory authorities may need to be increased.

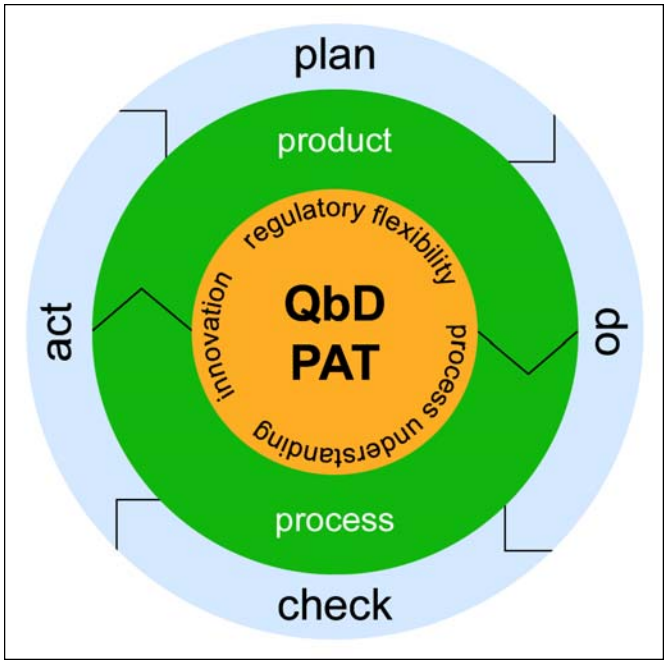

Figure 4. PAT circle developed by the COP for a better understanding of product and process.

  - The implementation of PAT within the organizational structure requires accountability, roles and responsibilities to be specified (clearly defined process owners, project managers, subject matter experts, and process analysts).
  - Depending on the structure of the company, employees working for a PAT project could remain members of different departments or be integrated in a separate PAT team or department.
  - Depending on the PAT approach (holistic or more specialized), an interdisciplinary project team with members from QA, R&D, Engineering, QC, IT, Manufacturing may be useful.

Implications on Management

The management also is involved since it has to support the PAT process.

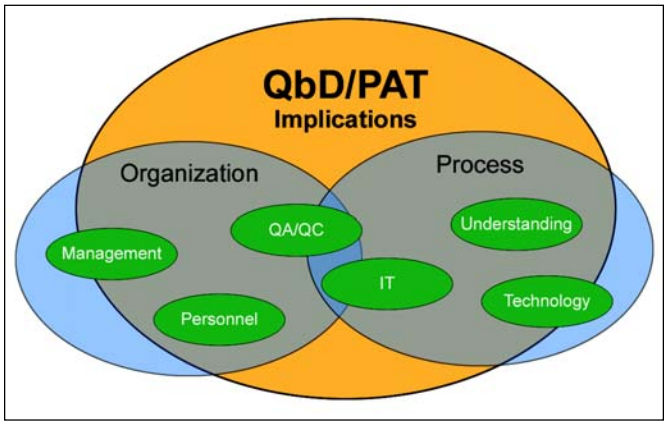

Figure 5. Categorized QbD/PAT approach implications and their impact on different business areas.

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- Commitment of management:
  - The management has to be committed to PAT to deal with the early phase of PAT, which could mean more investment.
  - However, in later phases, when processes are more efficient due to PAT elements, companies will be able to maintain quality at lower costs, and will be prepared for any future regulatory demands from agencies and thus be on top of the trend.
- Definition of PAT and development strategy:
  - Define the general approach.
  - Define the team.
  - Define which processes or products should be subjected to PAT first.
  - Define the goals and objectives and the expected benefits.
  - Plan and commit the resources (i.e., personnel, program money, equipment).
  - PAT means a paradigm shift from black/grey box to white box processes.
  - The development strategy may need to be revised; therefore, the specific requirements concerning PAT need to be analyzed.
- Risks concerning the company:
  - If PAT is ignored, there may be a risk of being left behind in the industry (competitive disadvantage) as well as a risk of image or business loss due to lower operational efficiency in sustaining reproducible product quality.
- Management objectives:
  - Regular review of benchmarks to stay on top of the project.
- Outsourcing:
  - Outsourcing partners need to be chosen and reviewed very carefully. Points to consider are:
    - their ability to perform projects according to PAT
    - knowledge transfer (content, interfaces, patents, etc.)
    - definition of accountabilities, roles, and responsibilities
    - communicational structure
  - There may be an increased need for secrecy agreements and/or more detailed contracts.
- Communication:
  - Communication between all kinds of different partners (e.g., departments ⇔ departments, vendor ⇔ company, company ⇔ agencies, etc.) may need to be intensified.

Implications on the QA Approach

- There may be an impact on the existing QA structure.
- Change in regulatory processes
  - With PAT, communication between regulatory authorities may have to begin earlier and become more regular (and possibly less formal).
- Audits
  - Regulatory scrutiny will challenge the scientific understanding of quality-relevant factors and how quality-relevant risks are mitigated. Developing departments will get increasingly more attention from regulatory authorities. Continuous improvement and a clear structure for documenting changes and deviations need to be demonstrated. Comparison between real design space and documented design space will be in the focus of an audit.
- Validation
  - Validation will be demonstrated by continuous measurement of critical-to-quality parameters in real/near-real time instead of the traditional three batch validation. The continuous validation process improvement will reduce today's validation efforts by more in-depth understanding of process variability in the future.
- Documentation
  - Better knowledge of the impact of raw materials may change specifications.
  - Specifications for submissions probably need to include design space and control space relevant to the product and process in which they are being used.

The QbD/PAT approach links together the four areas of Process Understanding linked to Risk Management, QA/QC, Technology, and IT – which clearly is at the core of the QbD/PAT paradigm shift.

By applying such an approach, the process is controlled and fully understood, and the right data for real time release enables continuous process verification and improvement via knowledge management.

B) QbD/PAT Impact on the Process

Impact on Process Understanding

- Development of process models:
  - The analysis of the process should define which parts have some flexibility (design space) and which are very rigorous.
  - In order to define system/process boundaries, (re-)structuring of complex processes may be helpful.
- Situation analysis is the evaluation of historical data for marketed products (from specification results, corrective actions).
- Impact analysis is the identification and evaluation of process steps, sources of variation, and the variables that are critical to quality.
- Critical process parameters need to be identified using appropriate techniques (e.g., FMEA, statistical analysis, risk analysis, and root cause analysis).
- Monitoring/controlling of the process through definition and implementation of relevant measurements. This is necessary to obtain data which can be reviewed for better process/product understanding and control.
- Verification of the control cycle is necessary to understand the impact of process parameters on process/product quality.

Impact on Production-Related QA/QC

- Specifications

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  - Quality control testing will evolve from testing against a discrete specification (pass/fail) to real-time comparison of process/product signatures against a reference. This reference will be a specification which will look totally different in a PAT approach as the process set values are flexible and based on a control strategy incorporating the design space.
- QC testing
  - Parametric release and in-line control could have an impact on QC headcount and work.
  - There may be a necessity for additional verification of parameters and definition of prerequisites for parametric release.
  - In order to recognize a slow deviation from expected requirements (e.g., raw materials, wear of materials, etc.), additional controls may be needed.
- Continuous improvement
  - Under PAT, manufacturing processes are monitored and controlled on-line, which – as opposed to a static process validation – leads to continuous process improvements. A continuous improvement and control of design space will be increasingly important.
- Equipment validation, including the control cycle
  - In contrast to the common validation approach, where testing the functionality of the immediate equipment is sufficient; with PAT, the complete control cycle of the equipment is included.

Impact on Process Technology

- Continuous production
  - New equipment may be needed to enhance data acquisition and process understanding. Better knowledge of the process could lead to continuous production and faster release.
  - Due to design space, production equipment could be used more flexibly.
- Availability of suitable sensors/methods
  - After the identification of critical process parameters, the availability of suitable sensors and methods has to be verified.
- Interface systems engineering ⇔ product engineering
  - Since all parameters of a process have to be well understood, system engineers and product engineers will probably have to work together more closely.

Impact on PAT-Related Data Management/IT

- New software/tools
  - New equipment, tools (e.g., SOA, XML), or applications may be needed to enhance data acquisition and analysis.
  - Infrastructure, databases, and software should enable easy data mining.
- New methods
  - New methods (e.g., MVDA, DoE, process modeling) including knowledge base maintenance must be implemented to enhance data and process analysis.
- Software validation
  - There will be increasing scrutiny on software validation at regulatory audits.
  - The requirement for complete validation of software may start even earlier during research.

Chapter 4: Approach to the PAT Awareness Project and Case Studies

The basis for the PAT awareness document was the evaluation of 11 PAT case studies. The assessment phase included interviews to achieve the best understanding of the executed PAT projects.

The identification and evaluation of benchmarking parameters concerning PAT applications is important for various aspects:

- to raise acceptance in the management
- to proof the maturity of projects
- for monitoring project progress

For this purpose, a catalog of standardized questions for evaluating and assessing the case studies was created. The following categories have been defined and considered for this assessment:

- Category 1: Quality
- Category 2: Process
- Category 3: Risk
- Category 4: Cost
- Category 5: Personnel
- Category 6: Tools
- Category 7: Time
- Category 8: Validation
- Category 9: Organization
- Category 10: Regulatory

In order to allow proper benchmarking, quantification is necessary, which is independent from absolute values and instead uses a rating that makes it possible to compare several projects. Thus, the answers were ranked from one (best fulfillment) to five (not fulfilled).

Case Study Evaluation and Results

Overall, 11 case studies were collected based on the issued questionnaire. These case studies originated from manufacturing and development sites of large pharmaceutical companies. Unfortunately, all persons interviewed about projects wanted to remain anonymous.

The evaluation results obtained for the individual evaluation categories are summarized below.

Assessment Category 1: Quality

The following benefits depend on the degree of the PAT implementation:

- OOS reduction
- better quality definition and analysis methods
- reduction of complaints and recalls

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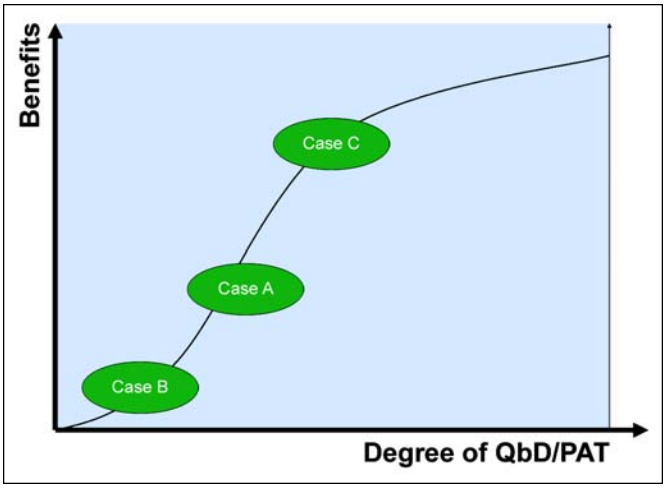

Figure 6. Case study evaluation revealed different benefits, but no quantifiable results.

Assessment Category 2: Process

In all investigated case studies, the general process understanding has greatly increased, e.g., by an optimized adjustment of known process parameters. In some case studies, new Critical Process Parameters (CPP) also were identified and used for advanced process control.

In most cases, the process cycle time was significantly reduced, while the productivity was increased.

Introduction and implementation of new process automation technologies – including sensors, analytical devices, and process control technologies – is not a mandatory prerequisite for QbD/PAT. QbD also can be achieved with existing process and control equipment.

The benefits of implementing QbD/PAT in the process have been estimated to be very positive.

Assessment Category 3: Risk

Risk assessment is a positive state-of-the-art methodology for risk detection and minimization, but currently in the companies sampled independent from PAT. Risk assessment will become a key integral method within PAT.

Assessment Category 4: Costs

Most of the case studies cannot give an answer to the question of ROI, and only one case study claims a ROI period of less than one year. In all other cases, it is still too early for a meaningful calculation.

Practical experience, as far as available, revealed fewer rejected batches, fewer deviations, increased yield with higher Overall Equipment Effectiveness (OEE), fewer consumables, less waste, and fewer reworks.

Assessment Category 5: Personnel

Up to now, there has been no reduction in personnel. Production is less lab-intensive due to a higher degree of automation, but the personnel has shifted their tasks to implement and improve PAT. The shift to PAT-based thinking encourages the communication between different departments. A better process understanding is obtained. There are hints to a slight increase in personnel safety.

Assessment Category 6: Tools

A clear result of the investigation is that more process data is recorded, analyzed, and stored. The data is additionally used within the batch documentation. In most cases, the data is used for advanced process control and the prediction of process deviations.

Applied analytical methods: NIR, MIR, Raman, laser diffraction, mass spectroscopy, accelerated dissolution testing, etc. Applied statistical methods: MVDA, DMAIC, etc.

Assessment Category 7: Time

In summary, faster processes have been reported:

- higher utilization of resources
- reduced lead time by reduced intermediate off-line testing
- faster decisions for on-line quality assessment and faster and earlier decisions on waste material
- due to automated data acquisition, shorter transition time from raw data to meaningful process information
- material variability is detected earlier

Assessment Category 8: Validation

In total, a lower effort for validation is expected, but more effort has to be put into facility, equipment, and software validation during PAT implementation.

Assessment Category 9: Organization

QbD/PAT projects have an impact on the organization of pharmaceutical companies and increase the interdisciplinary communication between departments.

Assessment Category 10: Regulatory

Regulatory issues have a strong impact on:

- the frequency of scientific-based contacts and communications with regulatory bodies

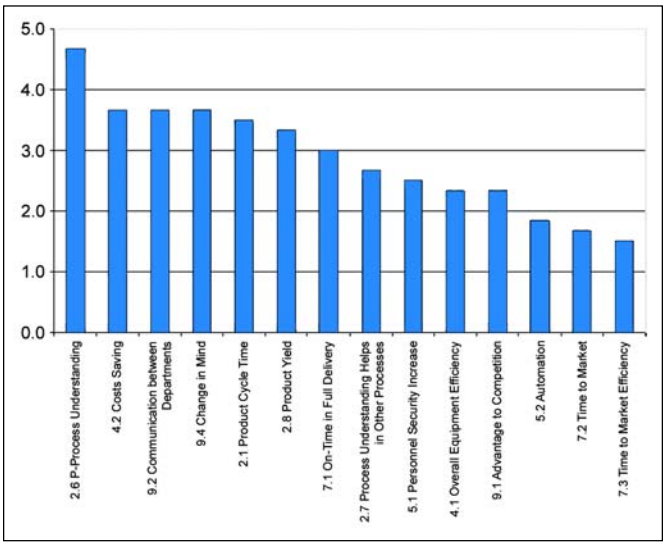

Figure 7. Identified and ranked benefits.

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- earlier and more frequent contact before and during the implementation phase
- the kind of documentation that will undergo changes (more precise and deeply science-based, earlier documentation during design is expected)
- change control (a positive impact is anticipated)

Management Summary of the Case Study Assessments

The quality, risk, validation, and regulatory aspects can be summarized as a positive experience when PAT is professionally implemented. Companies less experienced in PAT project implementation also have positive expectations, but need further practical experience before gaining tangible benefits.

Process understanding has strongly increased as well as the interdisciplinary communication between departments.

Generally speaking, a lot more data is stored due to the implementation of PAT levels of understanding; and the utilization of a broad variety of technologies. On the other hand, improved PAT data management offers the prospect for advanced and comprehensive data analysis and assessment. However, this potential has not been fully exhausted yet.

Currently, most of the ongoing PAT projects are not mature enough for any sophisticated calculation of cost benefits. However, experiences to date show decreased indirect costs, such as fewer rejected batches, higher yields etc.

With regard to costs, benefits are claimed in terms of higher yields, reduced cycle times, and fewer rejections/reworks rather than in terms of fewer personnel (who experienced a shift in tasks).

Conclusions

As the QbD/PAT management awareness is still low, the results will be presented to pharmaceutical companies to create QbD/PAT management awareness with the goal to initiate PAT projects. The COP already pursued this approach in one pharmaceutical company in Germany. The result was positive and supported the internal QbD/PAT discussions.

To bring the QbD/PAT initiative ahead, the focus should be on small PAT projects executed directly in manufacturing environments, and not on PAT-oriented submissions to realize quick wins. By starting with smaller projects, the full understanding of the PAT approach will slowly take root and the change for the industry will be easier and more gradual.

The regional PAT COP DACH group will continue their work and the main focus will be on providing a networking PAT platform for the ISPE members of Germany, Austria, and Switzerland. This platform will enable the industry professionals to exchange their technical expertise and experience.

The group also will support the upcoming activities the ISPE Product Quality Lifecycle Implementation (PQLI) initiative, recognizing that the QbD/PAT part is one important building block in the broader PQLI approach.

Figure 8. Practicing hands-on PAT technologies: analytical wine tasting at the "Schloss Vollrads" vineyard in Germany.

Glossary

API	Active Pharmaceutical Ingredient
CMC	Chemistry, Manufacturing, and Control
COP	Community of Practice
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CSV	Computer System Validation
DB	Data Base
DCS	Distributed Control System
DMAIC	Define Measure Analyze Implement and Control
DOE	Design of Experiment
DSC	Differential Scanning Calorimetry
EU	European Union
FDA	Food and Drug Administration
FMEA	Failure Mode and Effects Analysis
GMP	Good Manufacturing Practice
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IT	Information Technology
MIR	Mid Infrared (Spectroscopy)
MVDA	Multi Variate Data Analysis
NIR	Near Infrared (Spectroscopy)
NMR	Nuclear Magnetic Resonance (Spectroscopy)
OEE	Overall Equipment Effectiveness
OOS	Out of Specification
OTIF	On Time in Full Delivery
PAS	Parental Alienation Syndrome
PAT	Process Analytical Technology
PLS	Partial Least Squares
PR	Parametric Release
QA	Quality Assurance
QbD	Quality by Design
QC	Quality Control
R&D	Research and Development
ROI	Return on Investment
RTR	Real Time Release

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SOA	Service Oriented Architecture
SW	Software
WIP	Work in Progress
XML	Extensible Markup Language

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Acknowledgements

A group of volunteers worked on the contents of each chapter of the awareness document. Thanks to all participants for their creative input, for spending the time and putting in the effort to make this document possible.

Christian Wölbeling (Chairman)
Dr. Schmidt-Bader (Coordinator)
Lydia Dolezel (Coordinator)
Thomas Peither (Coordinator)
Dr. Christian Schmidt (Coordinator)

Dr. Rolf Altermatt
Dr. Rolf Bauer
Dr. Reinhard Baumfalk
Josef Braunschädel-Hilger
Dr. Jens Cardinal
Jeannette Ewen
Norbert Franz
Dr. Wolfgang Fischer
Georg Frinke
Dr. Jürgen Haas
Dr. Jörg Häußler
Steffen Himstedt
Dr. Thilo Jahr
Dr. Frauke Jordt
Prof. Dr. Rudolf Kessler
Dr. Wolfgang List
Joachim Mannhardt
Dr. Jochen Mohns
Karin Mühlfriedel
Thomas Peither
Volker Roeder
Dr. Marc Schiller
Dr. Ingo Symietz
Dr. Hans Tups
Michael Voß
Wolfgang Winter

About the Author

Christian Woelbeling is Director of Marketing and Sales at Werum Software and Systems AG based in Lueneburg, Germany with US headquarters located in Parsippany, New Jersey. He holds a Master's in mechanical engineering. Werum provides full-scope FDA/GMP compliant Manufacturing Execution Systems (MES) for pharmaceutical, biopharmaceutical, and fine chemical API production. Due to more than 15 years of experience in the pharmaceutical industry, Woelbeling has had great influence on the development of Werum's MES PAS-X product range. He has broad activities inside ISPE as board member of the ISPE Affiliate DACH, Chairman of the PAT-COP DACH and Co-Chairman of the global ISPE COP PAT Steering Committee along with John Levins. He can be contacted by telephone at: +49 4131 8900-49 or by e-mail at: woelbeling@werum.de.

Werum Software and Systems AG, Wulf-Werum-Strasse 3, D-21337 Lueneburg, Germany.

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Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2008, Vol. 28 No. 3

PHARMACEUTICAL ENGINEERING Interviews Ruediger Dorn, Managing Director, Worldwide Pharmaceutical Industry, Microsoft

by Rochelle Runas, ISPE Technical Writer, and
Gloria Hall, Editor, Pharmaceutical Engineering

In this interview, Ruediger Dorn discusses Microsoft's focus on the life sciences and the evolving relationship between plant operations and IT. Speaking from experience in auto manufacturing, he gives his thoughts on current challenges in the pharmaceutical industry.

Ruediger Dorn serves as the Managing Director of the Worldwide Pharmaceutical Industry as part of Microsoft Corp. In this role, he is responsible for developing and implementing Microsoft's global strategy, including the prioritization of industry solutions and their alignment to Microsoft's worldwide partners, regional, and local ecosystems. Additionally, Dorn manages regional vertical solutions units and engages with the sales and marketing teams for localized execution.

Prior to joining Microsoft in 2005, he spent nine years with the Oracle Corp. in various sales management, consulting, and business development roles. Between 2002 and 2005, he served as the (Europe, Middle East, and Africa) EMEA Industry Director for Life Sciences. He was responsible for Oracle's industry strategy for the life sciences market, as well as EMEA sales line of business solutions for pharmaceutical development. In addition, he built the services team offering consulting services into life sciences and worked as a business development manager for chemicals and pharmaceuticals in Europe.

Dorn joined Oracle from Accenture where he worked with product and strategy teams on customer projects in the chemical and pharmaceutical space. He also was involved in large re-engineering projects and served as the global project manager responsible for launching a new drug surveillance system at one of the largest pharmaceutical companies in Europe.

Dorn started his career at the central R&D IT Department of Robert Bosch, Europe's largest automotive supplier, and he worked in several IT functions, such as software development, database and server maintenance, systems design, and solution support. He holds an MBA degree as well as a Bachelor's degree in engineering.

Q Why is Microsoft focused on the life sciences?

A The answer's two fold. First of all, Microsoft is focused on industry in general. The life sciences is one vertical among other industries in the Commercial Sector. We are transforming our sales model from a traditional infrastructure business into a solution oriented business. We are adding additional sales forces and teams that understand the business requirements of our customers in the industry. It is an additional incremental effort we've been building for the last three to four years now and this is going to continue.

Second, the life sciences industry is particularly important to Microsoft as part of the extended healthcare environment. Readers may have heard of product announcements around Microsoft HealthVault, which is the electronic patient health record infrastructure, and a product called Microsoft Amalga, which is a hospital infrastructure. So, there is a broader investment scheme in place for the health industry and as part of the health industry, life sciences is truly strategic to Microsoft.

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Q As the Managing Director of the Worldwide Pharmaceutical Industry for Microsoft, what are your responsibilities?

A My main responsibilities are to define the industry strategy of Microsoft, which means define the solutions that we are going to build together with our partners all along the value chain. For example, whether it's collaboration in drug discovery and research, clinical trials systems, manufacturing execution, real time production, operation visibility, or sales and marketing, it's my responsibility to prioritize and define the solution areas we go after based on the market requirements and our customer demand. I then have my team work with the partners to build the solutions, because at the end of the day, Microsoft offers horizontal products, we do not offer industry specific solutions for the pharmaceutical industry. Hence we always create solutions in conjunction with a partner, for example, Aspentech, GE Fanuc, Invensys, etc. To corral these partners into a tight ecosystem is the key focus of mine and my partner managers.

I work with industry associations like ISPE, the Drug Information Association, and others, talk at conferences, educate our analysts, and brief the standard bodies in the industry.

Lastly, a key responsibility of mine is sales readiness. I give a lot of sales training to our field and I am involved in strategic sales cycles. My area of responsibility is diverse in that it involves very strategic thinking as well as very tactical activities.

Q Is Microsoft's focus on the pharmaceutical industry relatively new?

A Yes, on a global level, we've been focused on the pharmaceutical industry for nearly two years, and in the US, we've been focusing our efforts in the pharmaceutical industry for nearly five years.

Q What lead you into a career in IT for the life sciences?

A To be perfectly honest, it was by accident. The start of my career in life sciences was not planned at all. My degrees are in engineering and business and I began my career in the automotive industry in Stuttgart. Really, I used to be a discrete manufacturing guy.

During my tenure with Accenture, I began working in the life sciences industry and started to get excited about the complexity of the industry. I believe the reason for that was that life sciences deals with humans, that it deals with biology, and I always liked biology at school and never did anything with it afterward. Working in life sciences allows me now to talk to scientists about proteins in the genes, it allows me to discuss operational excellence with plant managers and to investigate new commercial models with marketing and sales executives. It gives me a satisfaction to help the industry meet the tremendous challenges and help improves the lives of patients.

Q Coming from the automotive industry and having worked in both environments, what are your thoughts on the challenges the pharmaceutical industry is facing and how those challenges are making life sciences look at other industries for solutions?

A I've seen both sides and to me it's almost like a déjà vu experience. It seems the pharmaceutical industry is now looking into problems and trying to solve those using techniques that the automotive industry has already applied for five years or longer. For example, Six Sigma is an established quality methodology in the automotive industry; it is not new.

I suspect the challenge for the pharmaceutical industry is that because of the relatively low cost of goods sold and the inherently large margins, there wasn't such a need to really focus on operational excellence in the past. All of the programs the automotive industry had to put in place because of increasing cost pressure and margin pressure, only now started to become relevant for the pharmaceutical industry who are faced with big patent expirations, drying up revenue streams, slowing down innovation cycles, etc. So increasingly the management realizes the savings potential in operations and the need to really apply some of the established concepts into pharmaceutical manufacturing. So I see a time lag between the automotive industry and the pharmaceutical industry, but also the opportunity for pharmaceuticals to avoid the mistakes previously made by other industries.

However, due to the different nature of process manufacturing versus a truly discrete process in automotive manufacturing, there are certain limitations in the way the pharmaceutical industry can actually deploy automotive concepts. In the market, a lot pharmaceutical companies look at Consumer Packaged Goods (CPGs) like beauty products, etc., because they tend to have a similar manufacturing process, and certain fast-moving consumer goods companies, like food and beverage companies, have been deploying Six Sigma, Lean, and just-in-time concepts for many years.

Q Obviously working in the automotive industry has given you good insight. Is there additional training and experience you feel really helped you in your position now?

A Ironically, I would say my A-level degree in biology has helped me. Because when you want to talk to researchers, for example, about personalized medicine and linking chemical entities to certain biological mechanisms inside your body, it is advantageous to know about the biology and the chemical background. Although, for the operations side of the business, the manufacturing process, my experience in the automotive industry has been far more valuable.

Q What are some of the Microsoft solutions for life sciences manufacturing that are helping customers speed up R&D and lower production costs?

A Microsoft solutions help customers to gain speed of insight and

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access to information. Microsoft provides solutions to people to bring data elements together, link them so that they are connected and make better and more agile business decisions. It is all about building information and knowledge and to make that knowledge accessible. The use case for this obviously differs, so e.g., scientists will use scientific information to do completely different things compared to plant managers, yet the concepts stay the same. Microsoft links different units inside an organization, beyond an organization with partners, and gives people access to one version of the truth to all the information they require for decision making. Better, faster business decisions is what really can improve business performance, both in R&D and in operations.

Microsoft's offerings concentrate on information integration, information accessibility, and then collaboration tools, tools that really allow people to work with other people to solve a project or a problem. It may be simple things like common files shares where users can find all documentation more quickly, business intelligence, instant messenger capabilities, up to highly complex solutions like integrated workflows and scorecards.

Q What would you say is the general state of information sharing in the pharmaceutical industry right now? Are there too many silos that are not linked together?

A There are still too many silos and while the industry is starting to link the islands of information, the challenge remains: How do you link information in a flexible agile manner and avoid hardwiring systems? It appears that often information – let's take DCS and MES systems on the shop floor – they are connected point to point, plant by plant by plant in different ways. Now imagine you want to change your equipment or your IT systems. You need to change that integration by touching multiple interfaces. The way forward for a very flexible and agile integration needs to be based on open standards and this thought is just emerging. Open standards are key to getting closer to the vision of a Service Oriented Architecture, i.e., a plug and play way to connect information bits and pieces together, and shape that knowledge that users require.

Q What about compliance and security – are there any products on the horizon for Microsoft?

A Compliance is a critical problem, and the solution to compliance ties back into what I said previously. Compliance regulations require a formalized process of doing things. One of the reasons why companies in the pharmaceutical industry may not be as far as in other industries is that they are obliged by the compliance rules and regulations to be able to document the process to then accomplish a process according to that specification. So there is an inherent challenge on compliance and how to implement flexibility and agility when compliance requires structure and stability. So compliance is likely going to continue to give IT managers a headache, yet there are tools on the horizon.

One very interesting tool is the concept of virtualization. With virtualization, instead of linking IT assets through actual interfaces, companies can now build up their application environment and system environment in a virtual way, which means it can be replicated to any machine. If someone needs to change it, the change happens centrally and a new version is made accessible to the users. All tests can happen once in the central test instance, IT specialists go through the validation steps, the compliance steps, and then make it available to everybody. Virtualization is a concept that can dramatically reduce the deployment of new systems, can reduce the cost validation, can increase the security because whatever you do it will be homogeneous and uniform all across the plants. And that is a big step forward.

Q In your experience, what has been the pharmaceutical industry's approach to IT, and do you think that approach can be improved?

A There is tremendous change happening in the industry and I see now projects where there is a direct involvement of central, the CIO office together with the heads of operations and the COO. We see an increasingly different approach to operations IT than in the past. In the past, many plant IT managers just made their decisions and built systems to cater to their business managers in the plants. Currently, more and more of our customers are frequently asking us for global architecture, for global systems deployments where they implement a uniform blueprint. That requires the CIO to be able to have a far deeper conversation with his or her colleague the COO, but the promise is to gain major improvements as far as IT effectiveness is concerned.

Q If you could imagine the ideal relationship between plant operations and IT (using examples or scenarios of daily life on the plant floor) what would it look like a decade from now? How close is the industry to achieving that vision? What challenges do we need to overcome?

A An ideal relationship between IT and the business requires mutual risk taking, regular interaction, and the measurement of true business value of IT solutions. In an ideal world, the IT and operations specialists would have constant interaction to update each other on latest technology changes, changes in the requirements, and agree on a joint IT strategy for the operations department in the company.

I don't think we live in perfect world here; however, looking at some of our large global customers and their global standardization efforts now on the plant level, I think the industry is on its way to achieving this vision.

One of the challenges to overcome is the interaction between different IT units and operations units, between different plants that used to be very autonomous and self-sufficient in the past. The vision requires a different way of working together, it mandates more interaction and more alignment, not just within one plant, but beyond one plant beyond countries on a global level. That needs to be based on a

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"One of the challenges to overcome is the interaction between different IT units and operations units, between different plants that used to be very autonomous and self-sufficient in the past. The vision requires a different way of working together, it mandates more interaction and more alignment, not just within one plant, but beyond one plant beyond countries on a global level."

different culture and thinking in a corporation and it's the cultural barriers that are probably the biggest ones.

Q What are your thoughts on knowledge management as it relates to the pharmaceutical industry? What are the best ways to manage the wealth of data and information our industry generates and uses?

A Knowledge management and its successful implementation is tightly linked to culture. If a company does not foster a culture of knowledge sharing, it may be difficult to demonstrate that wealth of information in the first place. It is typically difficult to get over the initial hurdle where users will question what is in it for them, so they are looking for benefits. And unless knowledge management is good enough to provide users with these benefits, they may not be prepared to feed the system back in with knowledge and information.

Q What is the future vision for Microsoft in the life sciences industry?

A Microsoft's future vision for the industry is to help the life sciences companies accelerate information, cut down costs, and get closer to the customers.

We have been developing our five year vision over the last six months and it will be formally communicated within the next couple of months. This longer term vision focuses on innovation, the cost effectiveness, and the commercial model of life sciences companies in order to help them sustain business growth.

The vision incorporates the challenges in the health industry and the fact that medical products will be far more individual in the future than they were in the past. It is unlikely companies will see blockbusters like the industry had in the past. The ultimate vision for personalized medicine is a one to one medicine that's just for the patient because it works against a particular genomic profile. Of course, the vast majority of medical products will cater for larger patient groups, albeit smaller ones than in the past.

Assuming smaller target patient populations, it's pretty obvious that the pharmaceutical industry has to rethink all of their business processes.

In R&D, the challenge will be how to develop innovative products when there are fewer patients for clinical trials. There needs to be much more profound information and knowledge about safety and efficacy of products against the particular genome and the particular protein predisposition of patients.

For the manufacturing process, it means a decrease in batch sizes. Taking the vision to the extreme, a truly personalized product is a discrete product manufactured for one specific patient. How are the plants of life sciences companies set up to manufacture that? And then how do sales reps sell that? Companies probably cannot sell personalized products to the doctor alone anymore. So the challenge for the industry will be how to collaborate with the health plans to show to them how a medical product adds value to the overall cost of treatment.

So the business processes are going to change significantly all across the value chain and the Microsoft vision now is to work with our customers to help them understand what IT can do for them in order to go through that transformation and how they can make first steps to get prepared. We want to educate our customers now so that they make the right decisions and won't have to change course in say three to five years when perhaps the patent expirations have exceeded another $50 billion.

Q How can Microsoft work with ISPE (in the future) to help us educate the community about the life sciences?

A Microsoft is a software vendor and we have a licensing sales model with our customers; however, I could see Microsoft and ISPE working together to educate the community in a better way to raise the awareness of information technology as a critical change enabler, but also as a critical support factor, for example, to achieve operational excellence. We are happy to help create awareness that it's not just about some IT system, but it's about a very people focused, a very role focused set of tools that needs to be provided to the people at the right time, at the right complexity, at the right user interface so that they can make actual use of the tool and exploit information technology for better business decision-making.

In that way, I can foresee multiple ways to collaborate with ISPE, e.g., we could collaborate to position information technology as a value added benefit to overall operations, not just a cost burden that people use to automate some processes. If Microsoft and ISPE can highlight the value of IT as a critical value generator and a change enabler for the operations business in life sciences, I would be very happy.

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The Official Magazine of ISPE
May/June 2008, Vol. 28 No. 3

Domain Methodology for Computer System Specification and Verification Applied to Manufacturing Execution Systems (MES)

This article summarizes the domain methodology described in the GAMP® Good Practice Guide on Manufacturing Execution Systems currently under development.

by Joseph F. deSpautz and Gregory Ruklic

Introduction

The ISPE GAMP MES SIG is developing a GAMP® 5 compatible Good Practice Guide (GPG). The group has examined the current state of computer software applications and systems with regard to product quality, recent regulatory initiatives, and the development of systems for life sciences. The examination has resulted in a generic methodology based on domains for defining, designing, and testing Manufacturing Execution Systems. This methodology is aligned to GAMP guidance and is independent of specific software applications being marketed to the life sciences industry. The methodology is described in the GPG and a summary is provided in this article

Current computer system applications often contain feature-rich functionality that crosses the enterprise and control levels[1] and expectations are that this trend will only increase. Typical descriptive application terms such as "business system," "Enterprise Resource Planning (ERP) system," "manufacturing execution system," and even "automation" may no longer fit the reality of the powerful and diverse applications and equipment in which various functions reside. This article presents an approach to encapsulate requirements and related functionality regardless of the system or systems in which it resides and apply the appropriate risk-based analysis to specification/design/purchase, integration, and verification required for GxP intended use.

The success of integrated systems projects can depend in part on taking advantage of proven industry standards and guidance. This article adds to the ISA-95 domain concepts to manage risk in the design and testing of integrated systems. Operational definitions and concepts are presented to acquaint the reader with key terminology and provide a foundation for applying the domain methodology to MES. For this article, MES is treated not as a computer system application, but as a collection of all the functionality used to plan, control, and execute manufacturing business processes with integrated computer systems.

While this article is based on applicability to MES, the concepts as defined and presented can be applied to complex or integrated systems in general.

Operational Definitions

Function – a group of tasks that can be classified as having a common objective.[1]

Functional Domain – a defined boundary around a set of system or application functions related to a common process/business function.[2]

MES Domain – comprises computer systems, applications, and equipment with related data and information that manage the processes, workflow, materials, and other resources to produce desired intermediate results or final products.

What is a Domain Methodology?

The word "domain" has several definitions as applied in various endeavors. The focus for this article is on organizing and documenting computerized systems and functions into groups or

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domains based on common attributes, business and manufacturing goals, intended use, or risks. In this article, the MES domain is the set of groups of functions from each component system, application, or equipment that is required to execute the intended business/manufacturing processes.

Each group of specific functions related to a business requirement can be assigned to a functional domain to help define interaction of the four major methodology components: information, personnel, materials, and equipment. This helps to identify both design requirements and testing activities based on processes, information flow, and regulatory compliance activities.

A functional domain may be viewed as a vertical slice down through the various systems/applications within the different ISA levels and infrastructure. Rather than attempt to classify a computer system or application as a single risk level, each functional domain within the system can be assigned the appropriate risk value or level to ensure that adequate and appropriate design/specification and verification activities are applied. For example, an MRP/ERP computer system may have functionality that is non-GxP, as well as functionality with varying levels of GxP impact. A single risk level is not appropriate as a basis for defining life cycle activities. It should be noted that system complexity defines the appropriate number and size of functional domains to be defined. For example, a single-task device or small system could be defined as a single functional domain.

Applying the domain methodology allows flexibility in testing methods to assess sets of functions (functional domains) based on categories of risk that apply. This ensures that documented specifications and tests are appropriate for the impact a particular functional domain has on product quality, data integrity, operational safety, and other critical criteria - *Figure 1*.

The example MES domain for this article spans real-time systems, such as automation, and through transaction-based systems, such as ERP. Depending on products, processes, goals, existing systems, and culture, each company, and perhaps each facility, may define their MES domain differently. Where possible, requirements are developed independent of the technology for implementation to ensure an objective definition of business needs prior to the selection of systems. However, it is more typical that one or more systems have been established in a company as standards that need to be incorporated into the MES domain. Differences in the overall implementation scope make MES projects challenging, interesting, and ultimately beneficial to companies that implement them. This approach drives standardization for efficient implementation and ease of understanding for support throughout their organization.

Why Use a Domain Methodology?

Since the publication of ISA-95, a common methodology in the life sciences industry has been to fit a particular software application or system into one of the levels one through four depicted in the ISA Functional Hierarchy Model. Developers and suppliers often attempt to position their system/application products based on these levels, without regard to implications for varying risks within a given system, across integration and verification, or for the intended use of the computer system functionality. Specific functions within a single computer system or application may indeed fall into different levels of the ISA Model.

The concept of Domain recognizes that inherent functionality within applications and systems often spans the Enterprise-Control System Integration layers.

Earlier testing methods based on GAMP categories tended to place an entire application into a single category, causing inappropriate risk values to be assigned to some functions, often resulting in either overly complex, or overly simple testing procedures to be applied to functions.

By assessing systems at the function level, each function or group of related functions can be analyzed and assessed for risk and design impact, assuring an efficient, appropriate, and consistent approach as described in GAMP 5. Analysis of process and manufacturing risks based on the risk to patients establish the boundaries and criteria that systems developers and testers must meet.

A domain methodology provides several benefits:

- allows concurrent design and test planning work to be defined and assigned to personnel or teams as soon as requirements are established
- encourages concurrent design of systems and test planning by establishing a design/test trace matrix immediately for each domain, providing a consistent approach to aligning design and testing activities throughout the project life cycle
- promotes understanding and documentation of system/application functions and the establishment of relationships among them during design and test planning
  - saves time in Change Management and Control by having an existing list of functions related to the desired change
  - facilitates or simplifies regression or other types of analysis in each case
- supports GAMP approach for mapping, testing, and verification to specification and design
- Functional Domains can provide framework to coordinate specification development during the design process for rapid design and implementation, as well as phased delivery, testing, and release of functionality in large systems.
- Risk values can be assessed more accurately by basing them in part on commonality of typical factors such as impact, frequency, and detection for the intended use of each functional domain.
- Applying domain concepts throughout the system development life cycle facilitates integration of interdependent entities and activities into a single design that meets criteria for the intended use:
  - manufacturing equipment, including process, computer, and automation
  - human and organizational activities such as training

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- information/data including documentation for each life cycle phase

Design Mapping for the MES Domain as an Example

Domain analysis and creation begins with developing the business requirements necessary to plan, control, and execute manufacturing operations, regardless of whether a company will develop or purchase new systems and applications, or integrate existing ones. Typically, it is some combination of both approaches.

Using material and product genealogy as an example, functions for material tracking, storing, testing/disposition, division (e.g., weigh/dispense), consumption, and creation of new inventory could be grouped into a functional domain. Such a functional domain can have several of the major functions in different applications. The risks associated with the functions will typically share many common risk factors

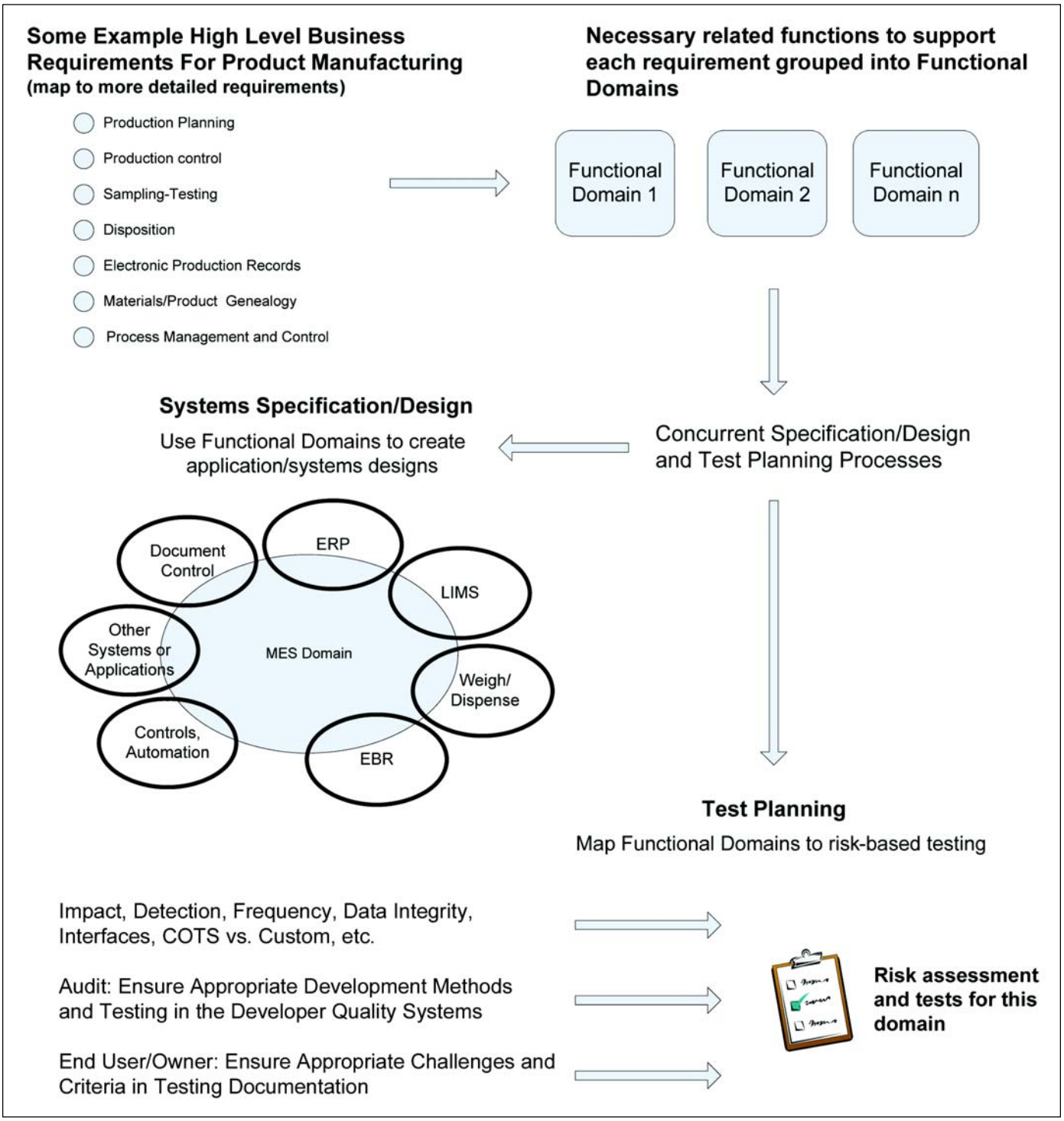

Figure 1. Applying domain concepts.

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so a consistent risk management approach can be developed for the domain. These risk factors impact the design of systems (redundancy, robustness), as well as types and complexity of testing, including any integration such as a built-in application interface (API), middleware, and equipment or data communications.

Systems can be specified, designed, purchased, and integrated based on each functional domain that is implemented by system components. The complexity and intensity of supplier audits can be determined based in part on the risk factors of the applicable domains.

Data should be considered in the domain creation and analysis process. The types and quantities of data associated with each functional domain can impact the domain risk factors.

Development of more detailed requirements and specifications can be part of the initial domain creation/analysis, or a result of domain analysis. Creating requirements, specifications, and designs is typically an iterative process, and the domain methodology is a tool to optimize risk management activities that are already part of any GxP life cycle process.

Note that requirements and specification documentation for systems and applications need not be much different than that used without a domain methodology. It is certainly possible, but not necessary to create separate documents for each functional domain. However, one can simply add cross references to existing styles of system documentation to establish the relationships. The complexity of systems and functionality often determines which method or combination is more efficient.

Applying the Domain Methodology to Verification

The basis for risk analysis and testing is primarily the intended use of the system, application, or equipment under consideration. Grouping related functionality into functional domains enables a more accurate assessment of specific risks related to activities undertaken with a given system or component. The domain methodology does not replace testing guidance described in GAMP 5, but supplements this guidance to improve the consistency of risk management, resulting in more appropriate verification planning and activities.

When functional domains are defined early in a project, whether for a new system or for changes or updates to an existing system, test plans and possibly some detailed testing method definition can begin almost immediately, concurrent with design and development.

Applying a domain methodology to support risk management promotes efficiency in defining and executing verification activities by reducing testing of functionality that poses a lower risk, and focusing resources on functions and activities that pose higher risk as identified in functional domain assessments. The domain methodology focus on functionality can unmask risks or risk factors which may not be as easily recognized with an application level or strict ISA level approach.

Typical risk management methods are applied to each defined domain to determine appropriate testing. The overall risk level for a domain is based on the influence of process, product quality, safety, and other critical factors, further modified by typical systems risks, such as level of customization versus COTS, and supplier audit results.

A company can further develop classifications of risk factors and associate them with specific functional domain types defined by common attributes. Functional domains with identical or highly similar risk factors can drive creation of standardized risk and testing management approaches resulting in higher consistency. Testing documentation can be written in modular formats to promote re-use among functional domains. As with any testing documentation, this can include automated test scripts, application-specific testing tools, logic and simulation test stands, or emulation applications to provide a realistic environment for testing.

For existing systems, prior testing is based on specifications which may not be oriented to domain functionality. Workload analysis of the effort for developing functional domains can determine whether a hybrid approach with and without domain analysis for various systems/applications can offer advantages or cause duplicate documentation. A hybrid approach could reduce or eliminate domain benefits for future development or change control, such as quick identification of functionality related to a change, or having comprehensive trace matrices from functionality to risk-based testing. Of course, the approach to testing each functional domain also is based on the process touch points and the associated process risk factors.

Testing for the MES domain may encompass one or more of the following:

- service Oriented Architectural platform for domain functionality
- self contained commercial applications that have API communications
- stand alone modules that are integrated by manual data entry
- custom software to address specific business process needs.
- Kernel product applications from a software supplier or systems integrator
- applications used to model business or manufacturing processes
- add-on configurable software packages such as historian, SCADA, batch processing engine, or multivariate analytical tool that would be used to develop Process Analytical Technology enhancements

Modular and integrated testing within a domain methodology should follow the GAMP guidance with test designs and phases linked to requirements and specifications.

Summary

The concepts in this article for applying domains in systems specification, design, and verification are further defined and explained in the upcoming ISPE GAMP Good Practice Guide:

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Manufacturing Execution Systems (MES) to be published in 2008.

The domain methodology can be viewed as a defined set of business processes, bounded by business objectives and success factors, to be executed by people, equipment, and information technology. The methodology focuses on business requirements and ensures that the implementing technology is appropriate at all levels for the intended use.

Applying the domain methodology can:

- enable an organization to integrate materials, equipment, people, and information while revealing and managing risks that can be hidden by looking at only the system or manufacturing model layer levels
- allow individual companies to define their MES domain based on specific needs and requirements in a regulated environment, and identify business processes or functions to be mapped to existing and/or new systems and components functionality
- foster cross-functional cooperation among systems, testing, and process groups due to the shared content and responsibilities of functional domains
- integrate risk-based design and testing at the functional level

Typical risk management approaches are applied to functional domains, resulting in a complete assessment and testing approach for the overall system/MES Domain. Organizational activities that are a part of the MES Domain are identified and grouped by the functions they perform and the dependencies they must support.

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Acknowledgements

The authors wish to gratefully acknowledge the following MES SIG members for their invaluable contributions during the creation of this article:

Karen Donaldson, Senior Manager, IT Compliance, Pfizer
Justin Iovino, Senior Consultant, BearingPoint
Paul Irving, Director, Aptitude UK
Ed Kanczewski, Principal Consultant, Process and Compliance Management
Kenneth S. Kovacs, Rockwell Automation
Allan Pfitzenmaier, President, Vectech Pharmaceutical Consultants, Inc.

About the Authors

Joseph F. deSpautz has more than 20 years of successful international experience serving in leadership roles in life sciences for MES applications, compliance, and LS manufacturing. He has held senior management positions for quality assurance, high technology medical device development, system integration, and commercial software development. At Rockwell Automation, he is a Senior Global Industry Consultant for Life Sciences – Asia Pacific. Prior to joining Rockwell Automation, he performed regulatory compliance and affairs consulting services for a biotechnology company submitting a Biological License Application to the US FDA. He has been a speaker at different pharmaceutical society meetings and has conducted many workshops at different symposia on 21 CFR Part 11, MES, EBRS, QA, system validation, Process Analytical Technologies (PAT), and IT systems for drug manufacture and clinical trials. He is a published author of many articles in life sciences manufacturing and the principle author and editor of Automation and Validation of Information in Pharmaceutical Processing published by Marcel Dekker, 1998. He is a member of ISPE GAMP MES SIG and the Editor of the ISPE *GAMP® Good Practice Guide: Manufacturing Execution Systems (MES)*. He has a BS in engineering from New York University, an MS in mathematics from Rensselear Polytechnic Institute, and post graduate studies in computer sciences. He can be reached by telephone: +1-852-288-4731 or by e-mail: jfdespautz@ra.rockwell.com.

Rockwell Automation Life Sciences, 6166 Gullstrand St., San Diego, California 92122, USA.

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Gregory Ruklic, Principal Engineer for Technology and Compliance, Wyeth Pharmaceuticals Biotech Operating Unit, has an extensive background of more than 24 years in the biopharmaceuticals industry with automation and integrated systems design, validation, and quality/compliance oversight working for engineering and quality unit groups. Ruklic has successfully implemented validated manufacturing systems internationally, and has held leadership positions in the development and implementation of site, operating unit and corporate level systems compliance standards and guidance. He is currently Co-Chair of the GAMP MES SIG, a member of the GAMP Americas Leadership Team, as well as a reviewer and contributing author for GAMP documentation, including the forthcoming ISPE *GAMP® Good Practice Guide: Manufacturing Execution Systems (MES)*. He was co-chair of the 2007 ISPE Washington Conference seminar on GAMP Validation of Automation and Computerized Systems related to Manufacturing Systems. Ruklic has presented at US and international forums on topics such as MES design in support of team-based manufacturing, and systemic (built-in) risk management. He can be contacted by e-mail: gruklic@wyeth.com.

Wyeth BioTech, 200 Ballardvale St., Building 1, 4th Floor, Wilmington, Massachusetts 01887, USA.

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PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2008, Vol. 28 No. 3

This article identifies ways to mitigate the risk associated with the manufacture of drug products.

Corrective Action Preventive Action (CAPA): A Risk Mitigating Quality System

by Gamal Amer

Introduction

As most everyone is aware by now, the FDA[1] issued guidance in August 2002 titled "Pharmaceutical CGMP for the 21st Century: A Risk-Based Approach; a science and risk-based approach to product quality regulation incorporating an integrated quality system approach." In order to fully appreciate the importance of the guidance, one needs to understand the following issues:

- What is risk and to whom?
- What events cause or increase the level of risk?
- How does risk manifest itself?
- How to define risk levels?

This article will attempt to answer these very specific questions before attempting to identify ways to mitigate the risk associated with the manufacture of drug products.

What is Risk and to Whom?

The International Conference on Harmonization (ICH) defines risk in Q9[2] as "The combination of the probability of occurrence of harm and the severity of that harm." Thus, risk is associated with detectable harm happening to an entity, which can be measured through a probability and severity. In the drug manufacturing process, risk is associated with an event that would compromise the quality, safety, and/or efficacy of a drug. Such compromised drug product could harm patients and the public in general. In some cases, the risk could affect the personnel manufacturing the drug, such as in the case where potent compounds are being manufactured. In other cases, the harm can befall the drug manufacturing company itself such as in the case where the company is found to be non-compliant with regulatory requirements and is assessed a fine or prevented from continuing to manufacture the product. In other words, risk is the probability of an event occurring, and it will occur, which would harm the patients, public, the personnel, or the company itself, and the severity of such an event.

This article will focus on addressing the risk to the public/patient that would occur during the manufacture of a drug, basically risk associated with Good Manufacturing Practice (GMP). It is the legal as well as the moral obligation of the drug manufacturer to reduce the probability of occurrence and to minimize the severity of harm when such events happen.

Risk Causing Events in Compliance

All human activities and endeavors have risk associated with them. Drug product manufacturing has quite a bit of risk associated with them. There is always the risk that contamination of the drug during manufacturing will result in harm to the patient who would use the contaminated or adulterated drug. During drug manufacturing, the occurrence of certain events, if not detected and/or mitigated, is a guarantee that harm to the patient will occur. For example, microbial breakthrough in sterile filtration of an injectable could lead to the contamination of the drug. If this is not detected and mitigated prior to administering it to the patient, it would result in harm to the patients being treated with the drug.

The microbial breakthrough, discussed above, is referred to as a quality event in the context of Good Manufacturing Practice (GMP).

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Quality events vary depending on the expected conditions, the type of operation, and their closeness to the end product. There are two types of quality events associated with risk in GMP compliance, namely;

1. Negative quality events resulting in increased risk, including:
   - patient complaints or suffering during clinical trial
   - operating deviation or processing nonconformities in manufacturing
   - analytical results not meeting the expected outcome in the laboratory
   - excessive effort needed to meet regulatory requirements

Such quality events require immediate positive action on the part of the manufacturer.

2. Non-negative quality events potentially increasing risk, including:
   - patient complaints showing a negative trend in post approval use of the drug
   - operation drifting toward action limit
   - analytical data trending toward the unacceptable.
   - repeated need to make corrections
   - results suggesting a need for further investigation

Such quality events require increased scrutiny and the development of a response strategy.

In all cases, these events have to be reviewed to determine their risk implications and a study has to be performed to balance the risk-benefit factors prior to implementing the proper action.

Risk in the manufacture of drug products ranges from a high or extreme risk level to a minimal or no risk level with the extreme having a "yes" and the minimal level having a "no" relationship to risk. In manufacturing, quality events are related to equipment and the operation of manufacturing systems. These go from the extreme of having direct impact on the product to the minimal of having no-impact on the product with several levels of having indirect impact on the product. The number of intermediate levels of risk varies from one organization or approach to another, and some organizations or risk assessment methodologies will identify three levels of risk, while others will identify as much as five.

Additional terminologies used to identify potential increased risk include critical system and non-critical systems, manufacturing equipment with product contact versus those without product contact. This is not to imply that non-product contact systems do not pose potential increased risk, but rather that issues associated with non-product contact equipment/systems are less severe and deserve less scrutiny than those associated with product contact equipment. Such terminology is important in defining compliance related activities such as commissioning and/or validation, types of actions to be taken such as corrective or preventive actions, and levels of interference such as rework or recall.

The next question when looking at such events is to identify how the risk manifests itself.

Risk Occurrence and its Manifestation

In the manufacture of drug products, some processes and/or operations are riskier than others. From a GMP point of view, the risk in these processes is dependent on the danger and its degree, which it poses to the public/patient when errors or defects occur and are not detected and addressed prior to distributing the product.

In the manufacture of drugs, the following processes/operations represent some of the riskiest in the business:

- sterile/aseptic processing
- potent compound processing
- labeling operations
- laboratory measurement errors
- operating errors in finishing operations
- automation systems, which rely on too many custom programs
- highly manual operations both in manufacturing and in record keeping

The risk associated with these operations manifests itself in many ways, including:

- contaminated drugs
- mislabeled drugs
- adulterated drugs
- drugs of the wrong potency (sub- or over potency)
- expired drugs
- nonconforming drugs
- non-performing drugs

Thus, it is incumbent on the GMP compliance practitioner to ensure that they are aware of all the risks associated with the operations they are responsible for. More importantly they should be aware of the way the risk manifests itself, ensuring a high level of detectability. Promptly addressing quality events as they occur and detecting the risk they pose are important components of any risk mitigating strategy.

Corrective actions as well as preventive actions are ways the drug industry uses to mitigate risk to the public. In order to develop the proper Corrective Action and Preventive Action (CAPA) quality system/strategy to mitigate risk, one needs to define and prioritize the risk levels in order to determine the proper action to be taken. Defining a Risk Probability Number (RPN) normally does this.

Risk Levels and the Risk Probability Number (RPN)

In the manufacture of drug products, the level of risk for a quality event can be identified through combining the **Severity** of the harm to the patient, the **Frequency** by which the event occurs, and the **Detectability** of the event. These three factors combined determine the level of risk either numerically or qualitatively as high, medium, or low. In order to

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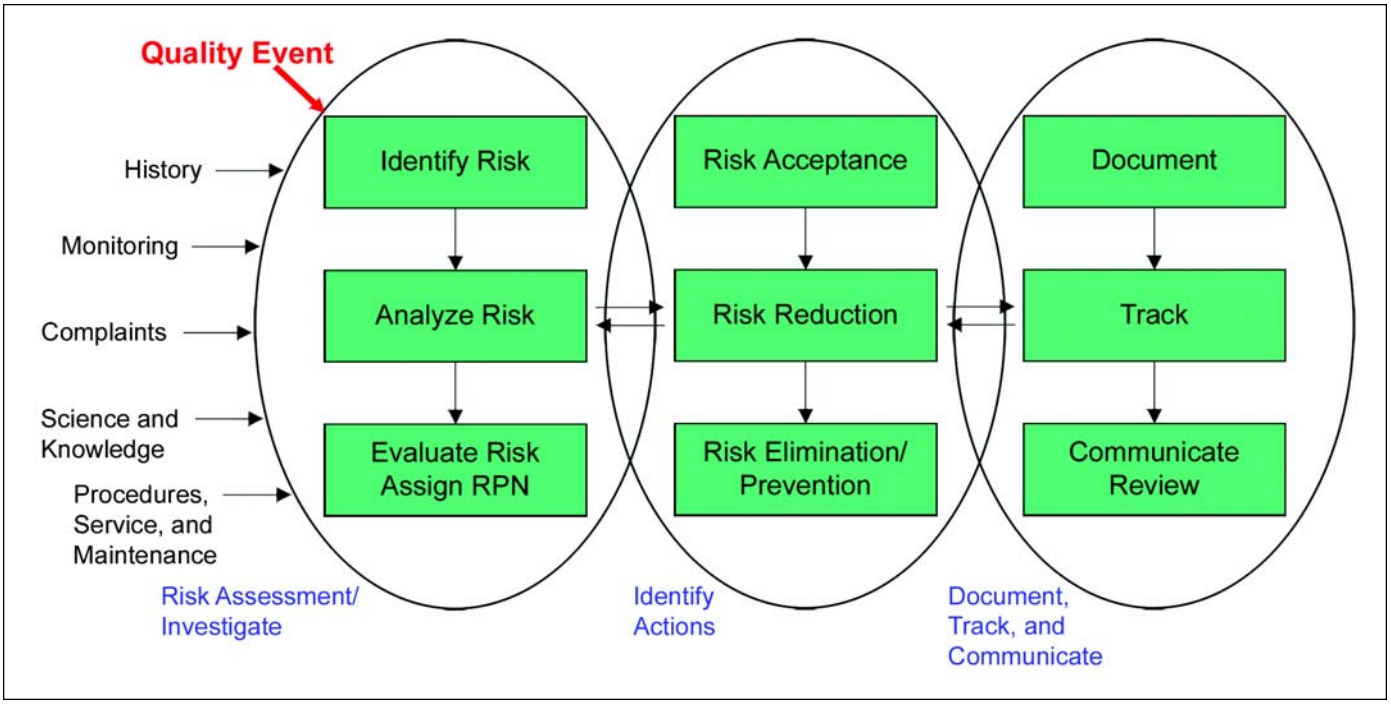

Figure 1. Overall approach for a robust CAPA Quality System.

reach a numerical value for the risk level, values to the three factors are assigned based on a company's experience with the product and the operation used to produce it. Multiplying the values for severity, frequency, and detectability results in a Risk Probability Number (RPN), which can be used to determine the appropriate Corrective and Preventive Action (CAPA) to be taken to address the quality event.

Severity of a given quality event is a measurement of the consequences of the event itself and its potential harm to the patient. The severity index ranges from events, which would result in a product causing death or serious injury to the patient (highest) to events causing no discomfort or delay of patient treatment (lowest).

Frequency of a given event defines the probability of its occurrence/reoccurrence. This is identified through reviewing the process history and acknowledging whether or not attempts were made in the past to reduce such frequency. The frequency index ranges from a certainty that the event will occur or has occurred frequently in the past (highest) to an event that is highly unlikely to occur or has been addressed in the past and preventive actions have been taken to prevent its reoccurrence (lowest).

Detectability is a measure of the probability that the quality event will be detected or its effect/result will be readily measured or seen. Here, events that are not detectable have the highest detectability index, while readily detectable events have the lowest detectability index.

Once the risk level for a quality event is determined, one needs to apply the principles of Q9, namely: "The degree of corrective and preventive action taken to eliminate or minimize actual or potential nonconformities must be appropriate to the magnitude of the problem and commensurate with the risks encountered." Thus, for low risk level events, normally no further investigation or corrective action is required. For medium risk level events, no further investigation (the cause is evident); however, corrective action is required. Finally, for high risk level events, further investigation (using Root Cause Analysis), corrective action, possibly immediate in the form of a recall, is required, and preventive action must be taken to ensure the event does not reoccur.

Based on this discussion, the risk level of a quality event occurring during sterile injectables manufacturing is very high, despite the fact that it does not occur frequently. This is due to the fact that it could lead to death (highest severity index) and is difficult to detect (highest detectability index). On the other hand, the risk level of an event occurring during the manufacture of an over the counter analgesic tablet is low even if it occurs frequently, because of the fact that its harm is low (low severity index) and its detectability is high (low detectability index).

Corrective Action Preventive Action (CAPA) – Mitigating Risk in Compliance

Corrective Action Preventive Action (CAPA) is a quality system designed to mitigate risk in the manufacture of drugs and devices. ICH Q10[3] suggests that pharmaceutical companies "should have a system for implementing corrective actions and preventive actions… structured approach to the investigation process should be used with the objective of determining root cause." As a risk mitigating quality system, CAPA addresses quality events, which occur during the manufacture of healthcare products. These could be a devia-

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tion, a failure to follow or implement an established requirement, a nonconformance failure to meet a specified requirement that occurs during the manufacture process. These quality events have the potential of posing a risk to the population and the need to mitigate their effect. In general terms, CAPA would define the risk resulting from such events and its level, identify an approach to mitigate such risk, implement the approach, and ensure its completion, while monitoring the implementation to ensure its success.

CAPA is a quality-based system, which uses deviations, nonconformances, and/or expectation of an event as the input to the system. It uses many of the quality procedures and systems already in existence within an organization to investigate and develop appropriate actions aimed at mitigating the risk. It also utilizes existing historical quality data, monitoring data, audit reports, service and maintenance records, product complaints, process knowledge, and operating procedures as a basis to identify risk and its level. Finally, once the actions identified are implemented, CAPA, by definition, has to track such implementation to ensure timeliness, correctness, and appropriateness.

In order to achieve its objectives, a CAPA program must investigate the event, identify its consequences, and track the implementation of what specific action is implemented. So, CAPA investigates the cause and potential risk of a quality event as it relates to the product, process, and the quality system. Quality procedures used for such investigation include deviation reporting and investigation procedures and Out Of Specification (OOS) investigation procedures. CAPA also investigates the potential risk of an expected or contemplated event. It also uses tools such as HAZOP, HACCP, Failure Mode and Effect Analysis, Fault Tree Analysis, and "What If" scenarios to investigate level of risk of an event, its cause, and/or its "root cause."

CAPA identifies the action needed to correct, reduce, or prevent recurrence of nonconformance of product and other quality problems. It also identifies the action needed to correct and prevent recurrence of the deviation in the operation as well as the action needed to prevent the potential occurrence of the anticipated quality event. These actions are generally referred to as corrective actions. Many of the corrective actions include one or several of the following:

- design changes
- manufacturing process changes
- removal of product from the market through recall
- operator training
- labeling changes
- patient education

It is of the utmost importance to recognize that whenever a change is contemplated, the change control procedure/system must be invoked. This will ensure that a record is maintained and that all quality, as well as GMP compliance implications, are reviewed and addressed.

Preventing the potential of deviations or nonconformances is also an objective of a robust CAPA program. Such measure is normally reserved for events, which have high Risk Probability Number (RPN).

Finally, CAPA tracks the implementation of the corrective/preventive action to ensure that the implementation of the action is completed on a timely basis and that introducing such changes do not introduce additional or new risk components. Tracking can be accomplished using appropriate procedures, while documenting everything associated with the event. Documentation of the event itself, the investigation and its findings, the action to be taken and timing for its implementation, closure of deviation or nonconformance are just some of the issues which must be tracked. Manual tracking represents challenges associated with generating too much paper, being cumbersome, time consuming, and providing limited access. Electronic tracking is becoming more and more common and eliminates many of the shortcomings of manual tracking. Today, there are several off-the-shelf products capable of providing such tracking functionality. However, these electronic tracking systems add the requirement of being 21 CFR part 11[4] compliant since they generate and maintain electronic records.

Figure 1 is a pictorial depiction of the general components of a CAPA System.

CAPA: Example Implementation

One of the most important examples of applying a successful CAPA is associated with the Tylenol® scare of the 1980s. The quality event was the fact that capsules of an Over The Counter (OTC) analgesic formulation were laced with a poison and were eventually ingested by the public and resulted in the death of several persons. Upon recognizing the harm that occurred, the manufacture conducted investigation and recognized that the root cause was someone tampering with the capsules, while on the store shelves and laced them with poison in a random fashion. At that time, the manufacture used a nationwide recall of all encapsulated product as Corrective Action (CA). Based on further technical investigation, the manufacturer reached the conclusion that there is no way a capsule can be protected from future tampering by a determined person. Therefore, the Preventive Action (PA) taken by the manufacturer was to eliminate the use of capsules in Over The Counter (OTC) products and shifting to the use of caplets. Since that time, capsules were no longer used as a dosage form for OTC drugs.

Upon review of this incident, one would recognize that the severity of the quality event was at the highest possible level (results in death); thus, one could assign it the highest possible severity number. Although the quality event itself would probably be infrequent with a finite probability that it will reoccur (it has occurred twice by that time giving it a frequency number that is relatively high), it would be very difficult to detect giving it the highest possible detectability number. The combination of highest severity, highest detectability, and high frequency number would result in a very high RPN suggesting the need for immediate corrective action (recall) and eventual preventive action (eliminating capsules as dosage form in OTC drugs).

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"...CAPA is a quality assurance system, which addresses quality events, which may occur or could be anticipated to occur during healthcare products manufacturing."

This also suggests that although the term CAPA was not in wide use in the 1980s, many drug manufacturers had in house programs to address such eventualities. The example here shows that the manufacturer of the analgesic has implemented a quality approach that resulted in protecting the public and preventing further risk to its welfare. Articulating the program based on the ICH and FDA guidance helps formalize such an approach and ensures that all drug manufacturers implement it. This ensures a higher level of safety to the public and improves process and product quality for the entire industry.

CAPA: System's Components and Specific Steps

Up to this point, the discussion has focused on risk in compliance and in a broad-brush fashion, the general approach of a CAPA program. The following discussion will review specific steps which must be taken when implementing a CAPA program.

As discussed above, CAPA is a quality assurance system, which addresses quality events, which may occur or could be anticipated to occur during healthcare products manufacturing. The system is based on reviewing the event and analyzing the risk associated with the event. It then assigns a Risk Probability Number (RPN) to the event upon which a decision is made to accept, reduce, or eliminate the risk all together. Once the decision is made, then appropriate action is taken. The event, the analysis, the decisions made, and action(s) taken are then documented, communicated, and tracked to ensure that they were correct, appropriate, and did not introduce different or additional variability/risk to the operation.

The quality event, either a deviation, a nonconformance, or an anticipated result is the input for a CAPA program. In order to perform the appropriate analysis of the event, one needs to review appropriate historic data, such as monitoring data, product complaint data, analytical data, scientific knowledge, previous process experience, etc. This review, combined with using the appropriate QA procedures existing within the organization (e.g., deviation reporting and investigation, OOS investigation, etc.) will define the risk and its implication. Once a certain course of action to address the risk is identified, procedures such as maintenance, rework, and change control are utilized to implement the action.

Based on this discussion, the following represents proposed basic elements or steps for a CAPA program and how they would be implemented:

1. Label and Segregate Nonconforming Product

When a nonconformance occurs, the resulting product or material should be packaged, properly labeled (e.g. Hold, Reject, Quarantine), and stored separately in a segregated space with limited access.

2. Tag and Lock All Equipment Involved in the Event

Equipment which may have caused the problem or may have problems, also should be tagged indicating that they are suspect and locked to prevent further use until an investigation has taken place and a plan of action is established.

3. Document the Event or Issues

Record the nonconformance on the appropriate report forms (deviation, OOS, etc.). Ensure that all studies and decisions made are fully and properly documented.

4. Investigate and Evaluate

Review the event and the circumstances surrounding it. Document relevant details as part of the nonconformance or deviation report. Evaluate risk to quality and link it to protecting the patient. Use RPN to help determine need for in-depth investigation and Corrective/Preventive Action (i.e., the effort, formality, and documentation should be commensurate with the level of risk and be based on science).

5. Take Necessary Actions

Make necessary changes to reduce risk or eliminate it. Ensure that change control is invoked when needed. Track and evaluate the actions taken to ensure that no additional or different risk was introduced.

6. Record, Communicate, and Monitor

Record all actions taken and communicate the results throughout the organization. This ensures that other parts of the organization would not face the same problem by taking preventive action. Finally, carefully monitor the process to ensure that it has not been negatively affected by changes.

Conclusion

In conclusion, quality events, which occur during the manufacture of health products, are always associated with a level of risk. A robust CAPA program is a regulatory requirement that defines the level of risk and how to mitigate it. However, one must note that implementing such a program is not limited to the regulatory imperative, but also makes good business and financial sense. A robust CAPA program would lead to better understanding of the process utilized and by identifying potential deleterious events that may occur and addressing them a priori, thus optimizing its operation. Additionally, enhanced product and process understanding

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will result in improved product quality followed by improving its cost structure.

Moreover, implementing a CAPA program not only has such a potential positive economic impact on the manufacturing process, but also would lead to better customer satisfaction and reduces risk to the public, which is a major moral imperative. It also allows companies to better plan and use their resources through a structured QA system. CAPA systems facilitate a better and more informed decisions making process by manufacturers, and its existence improves a company's compliance quotient (i.e., makes a company look good to the regulators).

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About the Author

Gamal Amer, PhD is Principal at Premier Compliance Services, Inc., management consultants for compliance and manufacturing operations performance in the life sciences industry. He holds a PhD in Chemical Engineering and has more than 25 years of experience in the pharmaceutical and related industries. He has held positions of increased responsibility with leading pharmaceutical, consumer product, and engineering consulting firms over the years. His experience includes comprehensive process design in bulk pharmaceutical manufacturing, biotechnology manufacturing, pharmaceutical solid dosage manufacturing, and containment of potent and radioactive therapeutics. He is also experienced with facility development for therapeutic products operations. Dr. Amer is a recognized expert in GMP compliance and validation. He has consulted for many of the leading pharmaceutical, biotechnology, and medical device manufacturers. He has lectured extensively in the US, Europe, Asia and the Middle East, taught many courses, and authored many papers which were published in peer reviewed publication. He is a member of ISPE, PDA, ACS, and AIChE. He can be reached by telephone: +1-610-584-9731 or by e-mail: vpainc@aol.com.

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On-Line Exclusive Article
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2008, Vol. 28 No. 3

This article provides history and trends for automated fill finish for injectable drugs utilizing isolator technology.

Barrier Isolation History and Trends – 2006 Data

by Jack Lysfjord and Michael Porter

As the journey in time of the technology of barrier isolation went from prototypes in the late 1980s to today, there have been questions regarding the need for benchmarking the usage of barrier isolator technology. Another way to say it is: what is everyone else doing in regard to this technology? This survey presents its history and trends. We have attempted to gather as much information as possible to use as a database; however, we also know that we never achieve perfection with all data. Numbers are as good as the data we get. They are not absolute. Trends are real and that is what should be used for comparison.

This is the fifth survey on the use of barrier isolators for automated fill finish operations that began in 1998. The surveys have been done only on the even years because of the energy content it requires by both the authors and the users. Manual operations in a glovebox are not considered. It is evident that usage of barrier isolator technology continues to become much more common in the industry.

In the advanced aseptic processing arena, a new relative has evolved called a Restricted Access Barrier System (RABS). Surveys for this technology were done in 2005 and 2007 and will be presented in another article to be published in a future issue.

Table A shows 304 total isolators (that we know of) in 2006 as well as the progression of number of units since 1998. Tables B to D show the major pharmaceutical region break outs for Asia, Europe, and North America. Figure 1 shows the global deliveries by year. Figures 2 to 4 again show deliveries by year for the three regions.

Some companies embrace technology while others wait. Figure 5 shows companies who have most aggressively embraced the use of isolators. Table E displays the increasing number of pharmaceutical companies using isolators. Tables F to H show the regional breakout information.

1998	2000	2002	2004	2006
84	172	199	256	304

Table A. Filling barrier isolators (worldwide).

1998	2000	2002	2004	2006
11	19	30	42	50

Table B. Filling barrier isolators (Asia only).

1998	2000	2002	2004	2006
57	85	97	116	146

Table C. Filling barrier isolators (Europe only).

1998	2000	2002	2004	2006
35	49	66	90	105

Table D. Filling barrier isolators (North America only).

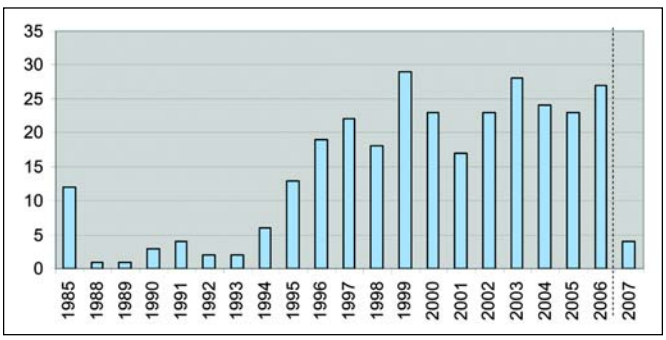

Figure 1. Barrier isolator filling lines – deliveries by year.

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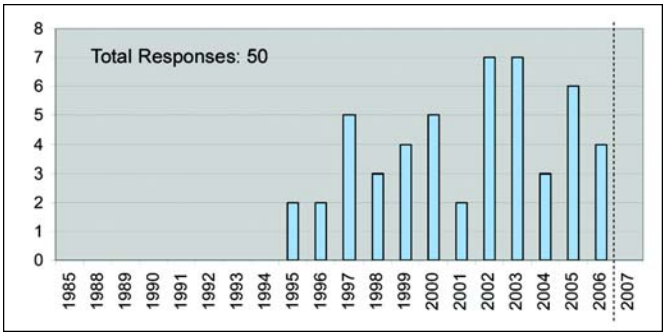

Figure 2. Barrier isolator filling lines – deliveries by year (Asia only).

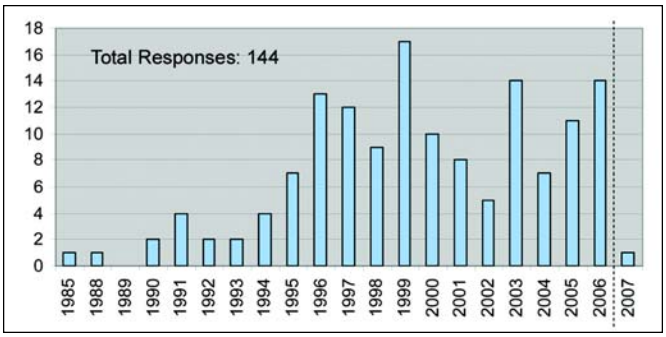

Figure 3. Barrier isolator filling lines – deliveries by year (Europe only).

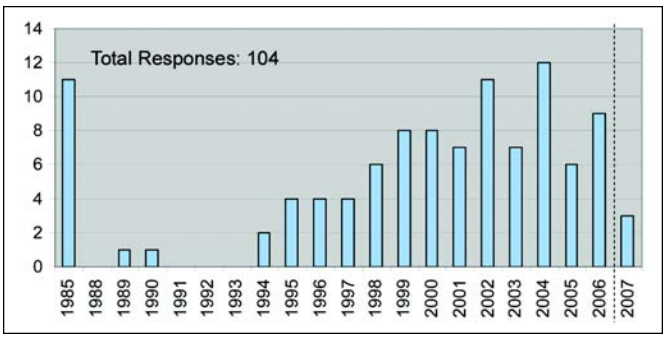

Figure 4. Barrier isolator filling lines – deliveries by year (North America only).

1998	2000	2002	2004	2006
32	56	67	83	84

Table E. Number of companies using barrier isolation.

Asia	Europe	North America
11	47	35

Table F. Companies using barrier isolation (by region).

1998	2000	2002	2004	2006
34	70	90	116	230

Table G. Barrier isolator filling lines – number in operation.

Asia	Europe	North America
38	102	90

Table H. Barrier isolator filling lines – number in operation (by region).

Container type is shown in Figures 6 to 9. It is interesting to see how, for example, the usage of ampules in Asia compares to Europe compares to North America.

Maximum line speed is shown in Figures 10 to 13. It is interesting to note that the majority of isolator usage in North America is for slow speed operation 0-99/minute.

Since 1998, the isolators have been hard wall (stainless steel and glass). Soft wall applications were used when the technology started, but reliability, pressure change issues, and sterilant absorption and outgassing pushed the manufacturing to hard wall design.

Surrounding room classification is predominately (61%) ISO 8 in operation with hydrogen peroxide vapor used in 84% of the reported applications for the biodecontamination agent.

Gloves can be one of the most scrutinized areas by regulators. Type of glove used is a decision to be made by users of the technology. Two piece gloves were preferred by 56% over one piece gloves 44%. If gloves are two piece, smooth sleeves are preferred by 84% over pleated sleeves 16%.

Glove replacement period data is in Figure 14 with some companies able to use gloves up to six months. Method of integrity testing gloves is shown to be predominantly by pressure decay - *Figure 15*. 83% of responses indicated usage of a second thin glove with the glove port (typically placed on the hand prior to entering the glove port).

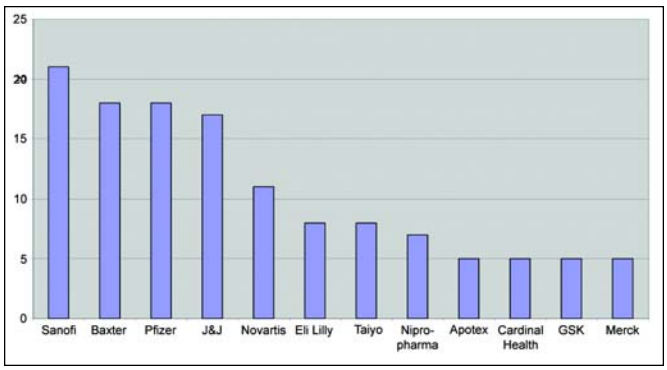

Figure 5. Barrier isolator filling lines – companies with highest usage.

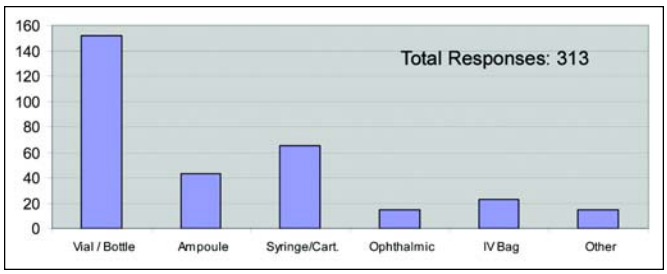

Figure 6. Container type.

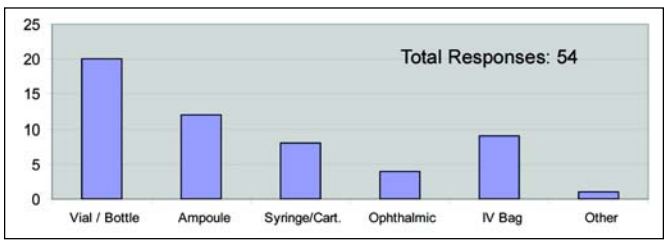

Figure 7. Container type (Asia only).

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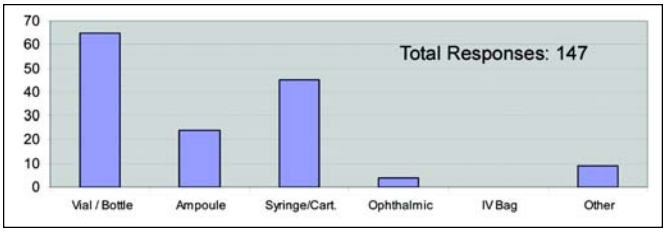

Figure 8. Container type (Europe only).

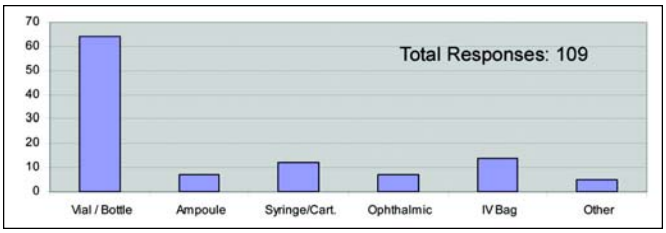

Figure 9. Container type (North America only).

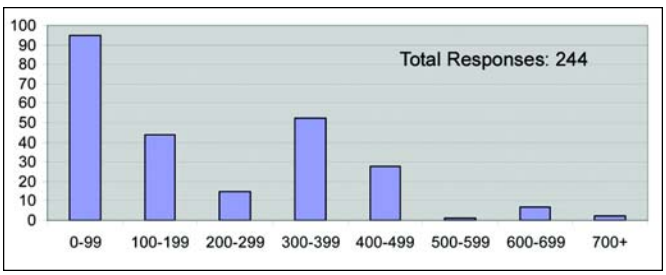

Figure 10. Maximum speed.

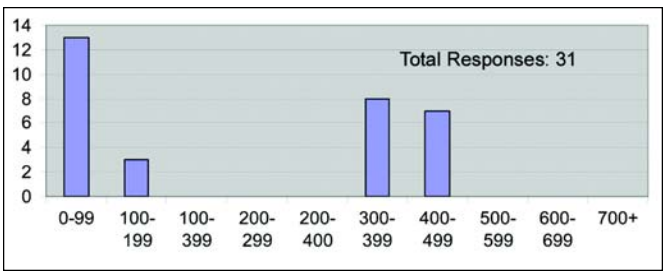

Figure 11. Maximum speed (Asia only).

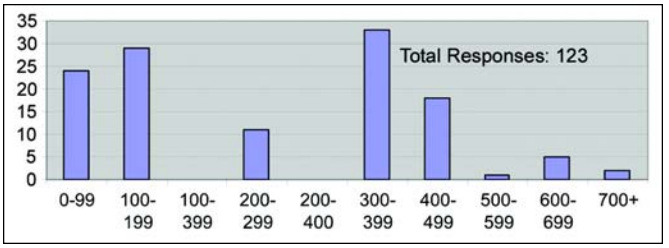

Figure 12. Maximum speed (Europe only).

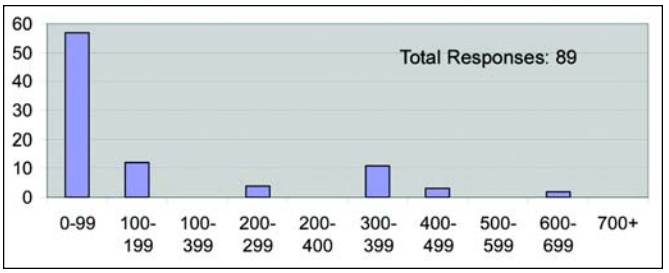

Figure 13. Maximum speed (North America only).

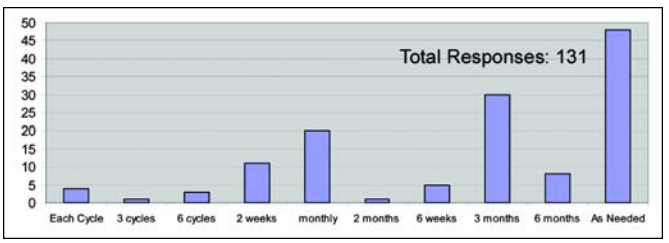

Figure 14. Glove replacement period.

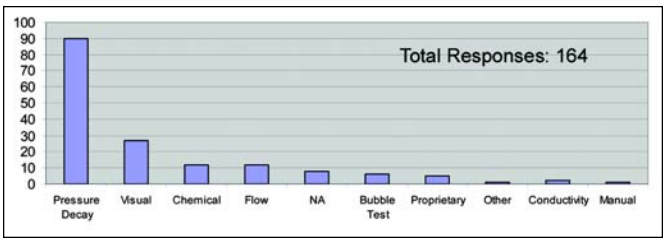

Figure 15. Method for integrity testing of gloves.

Positive overpressure is typically used in these applications. The concept of "more is always better" does not apply to systems with mouse holes at exits or depyrogenation tunnels that are interfaced with the isolator. Too much overpressure can "blow" the tunnel hot zone air into the washer and melt many parts. Small vials can be blown out of mouseholes destroying the product. Figure 16 indicates that the majority of applications operate between 20 and 39 pascals (more likely, 20-30 pascals due to how we asked the question).

Tunnel sterilizable cool zone technology was used by 49% of those responding.

Containment was a requirement on 35% of total responses in the five surveys. The data with this question must be looked at on a survey by survey basis to look at percent of containment needed on these responses for a two year period. 61% of 2006 responses (since 2004) indicated a containment need.

51% of responses indicated that they campaigned product fills within one isolator sterilization event. Figure 17 shows the length of campaign from the responses. The maximum campaign is 28 days.

Finally, cumulative deliveries of isolators are shown in Figure 18. We believe that isolator usage is increasing even faster than shown at the time of writing this article based on equipment manufacturers comments.

The Trends and conclusions are:

- Worldwide increase in filling line isolators continues (304) with significant increase in Europe (30) from 2004.
- Japan (8) and North America (15) showed moderate growth in two years.
- Isolators are embraced by some companies and avoided by others.
- Mergers and consolidation impact the number of user companies.
- Number of reported isolator lines in operation almost doubled (116 to 230) in two years.

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- Vials continue to be the predominant container.
- Hard wall isolators continue to be the preference.
- Smooth sleeve gloves are even stronger than in 2004 (84%).
- Slight preference for two piece gloves (56%).
- Use of a thin second glove is very strong (83%).
- Containment need is increasing (35%) (61% in last two years).
- Campaigning is increasing (51%).

Benchmarking information for those companies investigating the use of isolators is shown below (strongest preferences from survey):

- hard wall isolator
- biodecontamination technology hydrogen peroxide vapor
- ISO 8 in operation surrounding room classification
- gloves only, meaning minimize use of half-suits for interventions
- two-piece gloves with smooth sleeves
- use of a thin second glove
- doing glove integrity tests

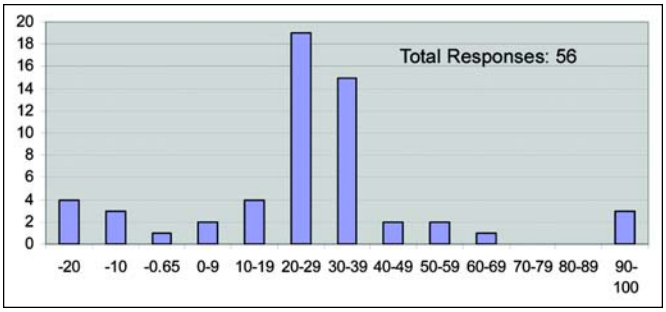

Figure 16. Pressure to washer rooms (12.5 Pascals = .05" Water).

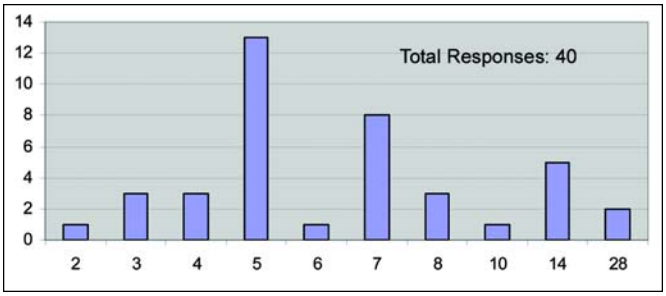

Figure 17. Campaign products (longest run).

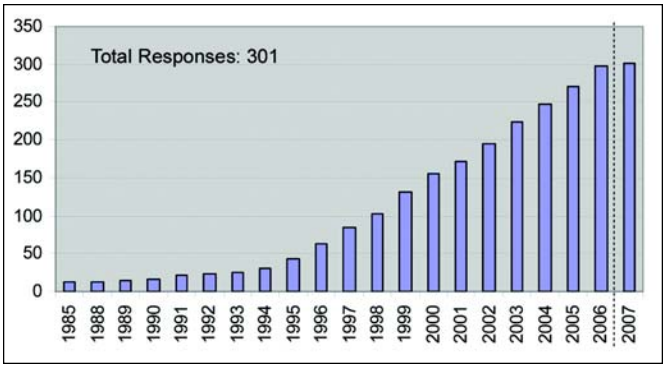

Figure 18. Barrier isolator filling line – cumulative deliveries.

Capital equipment technology and the accompanying depreciation expense last a long time. Remember that today's decisions will impact the company for 15 to 25 years. Look at what is in the pipeline for R&D to make a decision that will cover future products. Many product candidates will have the need of aseptic processing and containment in order to protect both operators and product.

About the Authors

Jack Lysfjord is Principal Consultant for Lysfjord Consulting LLC. He was previously, vice president of consulting for Valicare, a division of Bosch Packaging Technology. For more than 26 years, Lysfjord has held a variety of management positions with Bosch Packaging Technology (formerly TL Systems Corporation) that produced aseptic processing equipment for producing injectable drugs. Prior experience was with Dahlberg, Litton, Medtronic, and Onan (Dahlberg and Medtronic provided seven years medical device experience). Lysfjord is a member of ISPE, Parenteral Drug Association (PDA), American Association of Pharmaceutical Scientists (AAPS), the American Glove Box Society (AGS), the Parenteral Society (UK), the Isolator Users Group (UK), R3 Nordic (Nordic Cleanroom Processing Society), and Barrier Users Group Symposium (BUGS) of which he is Chairman. He is a frequent speaker and course leader on the topics of aseptic processing, RABS, and barrier/isolator systems in the US, Europe, and Asia and has been the author and co-author for numerous technical papers and articles. Lysfjord is currently managing and editing a book "Practical Aseptic Processing: Fill and Finish" that will be published in late 2008. He holds a BS in mechanical/industrial engineering from the University of Minnesota and an MBA from the University of St Thomas. He can be contacted by e-mail at: jlysfjord@q.com.

Lysfjord Consulting LLC., 2711 Sylvan Rd. S., Minnetonka, Minneapolis 55305-2821, USA.

Michael Porter is a Director in the sterile process technology and engineering group of Merck & Co., Inc. Since 1987, he has held a variety of divisional engineering and supervisory positions within Merck's Manufacturing Division, focusing on manufacturing, lyophilization, and barrier isolator technology filling of vaccines and sterile pharmaceuticals. Porter is currently responsible for start-up of a new vaccine manufacturing facility in Durham, North Carolina. He has prior experience in plant and process design in the petrochemical industry, and holds a BS in chemical engineering from Villanova University. Porter has been Co-Chair of the ISPE Barrier Isolation Conference for more than a decade. He is a member of ISPE, and has presented on the subjects of barrier isolation and cleanroom automation technologies dozens of times to the pharmaceutical community. He can be contacted by e-mail at: michael_porter@merck.com.

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The Official Magazine of ISPE
May/June 2008, Vol. 28 No. 3

GAMP® 5 Debuts to a Record Breaking European Audience

by Gail Evans, ISPE Technical Documents Writer/Editor

The GAMP 5 Seminar opened on Monday, 7 April, to a record breaking audience of almost 400 attendees - the largest single audience ever for this type of ISPE event. Peter Robertson (AstraZeneca), Chair of the GAMP Europe Steering Committee, opened what he described as a "truly momentous occasion" – the launch of the newest revision of the GAMP Guide: GAMP 5.

As part of his introduction Robertson gave attendees an overview of the aims of the ISPE GAMP COP, namely to:

- minimize risk to patients
- minimize compliance related costs

As a global group, this GAMP 5 European Launch conference is one of several, the first having been held in Tampa, Florida, and a second more recently in Turkey.
Robertson then introduced the first speaker: Dr Guy Wingate (GlaxoSmithKline), Chair of the GAMP COP, who had recently returned from the launch of GAMP 5 in Turkey.

DAY ONE

The Need for GAMP 5

Wingate explained why and how GAMP 5 had materialized. The GAMP COP had spent many hours deliberating whether there was a need for such a major rewrite of GAMP 4, which was both very popular and widely accepted within the industry. In addition, GAMP 4 is referenced from both the FDA and PIC/S documents.

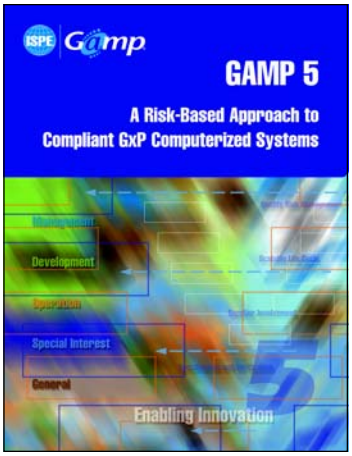
However, there were many drivers for the revision, but a prime consideration is that future GAMP activities will focus on areas where they can add most value to established industry good practices and adding value is central to this revision of the GAMP Guide.

Key drivers came from both industry need and regulatory changes – including the FDA 21St Century Risk and Science-based initiative and ICH Q9 Quality Risk Management, along with Q8 and Q10. Additional drivers include ISPE's own PQLI initiative and the ASTM Standard E2500.

GAMP needs to keep up with such changes in order to continue to serve industry and provide practical guidance, not simply to achieve compliance, but as a good practice and to provide clarity, scalability, and acknowledge that traditional models may not always provide the best fit in this new climate.

Wingate explained the process for developing the GAMP Guide - thanking all those who took time to contribute to the Guide and to review and provide comments on the draft that was made available for global industry comment.

Following Guy was a speaker form the UK MHRA, Andy Cochrane. Cochrane discussed the introduction of the updated GMP Annex 11 document, including the introduction of the concept of risk assessment in the decision making process. (Proposed revisions to Chapter 4 and Annex 11 are now available for comment.) Cochrane explained the reasons behind the proposed revisions and described the process by which such revisions are developed.



GAMP 5 Key Concepts

Sion Wyn then introduced the five Key Concepts, which underpin GAMP 5.

These Key Concepts are:

- Life Cycle Approach within a Quality Management System (QMS)
- Scaleable Life Cycle Activities
- Process and Product Understanding
- Science-Based Quality Risk Management
- Leveraging Supplier Involvement

Wyn's presentation provided an overview and background on each of these key concepts, which were later expanded upon by other presenters.

In addition, Wyn also provided details of the Specification and Verification approach provided in GAMP 5. (See Figure 3.3 from Main Body of GAMP 5)
"Specification steps have equivalent verification steps to determine whether the specification has been met."
The approach provided is not prescriptive in its terminology nor tied to traditional qualification terminology. The approach can be scaled to fit and some practical examples for typical types of systems were provided. These were based on the GAMP Categories 3, 4, and 5.

Wyn went on to discuss efficient and effective compliance. This included efficiency improvements, such as using risk-based decisions and leveraging supplier input and existing documentation. Efficient testing practices were considered, such as determining existing test evidence and ways to potentially reduce the overhead associated with testing practices.

In conjunction with Wingate's earlier presentation, Wyn's information provided the basis on which GAMP 5 was developed, some basic knowledge of the GAMP 5 approach, and set the scene for the presentations following during this two day launch event.

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Risk Management and GAMP 5

The first presentation was given by Randy Perez (Novartis), Chair of GAMP Americas, who explained how to use science- and risk-based management to implement compliant computer systems.

There was a traditional goal of trying to achieve *zero risk* – this has transformed to a goal of achieving *acceptable risk* during the last decade. GAMP includes a variety of tools and methodologies useful to companies who want to leverage a risk management approach to computer system compliance.

Perez discussed the GAMP proposed 5 step approach to developing compliant computer systems. The industry wants to focus its efforts where risk is highest and by doing so reduce (or even eliminate) work on low risk issues. This is supported by the FDA's cGMPs for the 21st Century Initiative which gave the message to use a reasonable risk approach. However, this leaves the question of how to define risk.

Perez explained risk management principles and the objectives of a risk-based approach, linking this to risk addressed throughout the process. The thought is that risk management permits an efficient allocation of resources to achieve an appropriate level of control that aims for low risk, rather than no risk.

There are several key considerations for the GAMP approach to risk management; these were discussed and placed in context of a clearly defined scalability strategy, which is considered crucial.

The GAMP categories provide a useful broad indicator and a tool for scalability and can be used as a factor in planning test rigor. There were several changes from GAMP 4 to GAMP 5 noted, particularly the removal of the old GAMP Category 2 – Firmware.

Perez cautioned that the categories had to be used correctly – false assumptions need to be avoided, such as a system which falls into Category 1 will always be lower risk than a system that falls into Category 5.

He went on to discuss the 5 step Risk Management Approach in GAMP 5 – working through each step in turn using a spreadsheet tool as an example. Ultimately, this was tied in with a control strategy based on risk and impact. Part of Perez's core message was that the process is consistent with ICH Q9.

User and Supplier Responsibilities

In the next presentation 'User and Supplier Responsibilities,' Tony Margetts emphasized the need for an organizational and governance framework in the regulated company, identifying key elements for this to be successful.

Margetts discussed the responsibilities of specified roles, such as subject matter experts and the Quality Unit. The next section of the presentation focused on the key concept of Leveraging Supplier Involvement. He explained that suppliers should use good practice and that in many ways suppliers may be able to offer more than a regulated company expected, including knowledge and experience of a given product. The suppliers' responsibilities were discussed and important elements, such as a supplier QMS and documentation. The importance of supplier assessment also was emphasized.

Aligning GAMP 5 with the GAMP Good Practice Guide: Validation of Process Control Systems

The last presentation of the day was given by Mark Cherry (AstraZeneca), who explained the principles and status of the revision to the GAMP Good Practice Guide: Validation of Process Control Systems (VPCS).

Much work is being done to ensure that it aligns with the new concepts presented in GAMP 5 and those in the new Specification, Design, and Verification Baseline Guide, along with the PQLI Initiatives. The revision embraces the risk- and science-based approach.

There are common principles adopted by GAMP 5, VPCS, and the Specification, Design, and Verification Baseline® Guide. The principles in GAMP 5 will not be repeated in VPCS, but instead the content will focus on providing examples to highlight the specific considerations for Process Control Systems, and how to apply the risk-based scientific approach. A much greater linkage to the Installation and Verification Baseline® Guide will be included- achievable because of the concurrent production of these documents.

Analogous to the development of GAMP 5, the VPCS revision aims to add value by focusing effort appropriately, avoiding duplication of activities, and leveraging supplier activities. Cherry worked through examples to show how the VPCS Guide could apply the 5 step process from GAMP 5 to a Tablet Manufacturing Process.

The next steps in development of VPCS, including the availability of a draft for review later this year, were discussed.

The day ended with a question and answer session with a panel of presenters and members of the GAMP COP providing answers and facilitating discussions.

DAY TWO

Practical Workshops on Scaling Life Cycle Activities

Day two commenced with an introduction from Wyn, explaining how the day was to be structured, including practical workshop sessions on scaling life cycle activities. Kate Samways (KAS Associates) kicked off the session by explaining how control could be maintained during operation, and the heavily revised and restructured O Appendices of GAMP 5 provide relevant information.

In addition, it was announced that a new GAMP Good Practice Guide on Maintaining the Validated State is in development and this document and its current status were described.

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The operational phase will likely be the longest single phase of a system's life and throughout it needs to be maintained in a state of control. The presentation identified the key operational procedures which are likely required, how they have been grouped in GAMP 5, and the relationships between the procedures.

Following Samways, Ellis Daw (GSK, US) presented a case study on Effective and Efficient Compliance. This provided attendees with a real life example of how the GAMP 5 Key Concepts and Approach could be implemented. Although there are many inputs to assist in deriving a process by which to achieve compliance – Daw concluded that GAMP 5 will be a tremendous help.

Some of the details required for implementation of risk management approaches to computer validation can be quite challenging. There are common pitfalls in the application of risk management which can be avoided and among the aspects providing a foundation for success are good practices, clear criteria, and a clear and simple process.

Daw underpinned these ideas with examples of an enterprise resource planning system and a laboratory system.

An interactive workshop session was held and attendees were able to try and apply what they had learned during the previous sessions.

The session began with a short presentation to 'set the scene' and to briefly reiterate key messages from earlier presentations. Scalability is about determining 'how much is enough' and for many this proves a challenging question. GAMP 5 provides tools, such as categories, and risk assessment and mitigation, to assist in making a determination. One key question is: "What adds value?" This impacts on documentation which should contain all the required elements to demonstrate that a system has been validated and is in a state of control.

As the workshop worked through each stage of the process, attendees were provided suitable responses to determine an appropriate combination of documentation for the given system.

Since approximately a quarter of the attendees were new to ISPE/GAMP, this proved to be a particularly useful activity, reinforcing the ideas contained in GAMP 5.

GAMP 5 and Electronic Data Archiving

The final presentation was provided by Per Olsson (ABB), who explained Electronic Data Archiving in relation to GAMP 5. The presentation was based on the GAMP Good Practice Guide on this subject. There are no readily available solutions for EDA that are guaranteed to stand the test of time and the Guide provides an introduction to developing an electronic archiving strategy and a template for developing such a strategy.

The launch ended with a second question and answer session with the panel of presenters and members of the GAMP COP providing answers and facilitating discussions.

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The Official Magazine of ISPE
May/June 2008, Vol. 28 No. 3

Introduction to ICH: Essential Background to PQLI

by Dr. Kate E. McCormick, ISPE European Education Advisor

Editor's Note: *The session, "Pre-Meeting for PQLI Workshop – Introduction to ICH," was held at the ISPE European Congress on Innovation in Copenhagen on 9 April. The session was meant to introduce ICH Guidance Q8, Q9, and Q10, perspectives from regulators in all three ICH regions of Europe, USA, and Japan, and give essential background to the objectives and considerations of PQLI before the PQLI sessions on 10 – 11 April.*

The following are key messages and highlights from the Introduction to ICH session:

Welcome and Introduction

Jacques Morénas, Associate Director of the Inspectorate and Companies Department of the French regulatory agency Afssaps and Chair of PIC/S, shared a platform with senior regulators from all three ICH Regions: Jean-Louis Robert from Laboratoire National de Santé in Luxembourg; Moheb Nasr and Joe Famulare from the US FDA; and Yukio Hiyama from MHLW in Japan. The workshop was chaired by Bruce Davis (Astra Zeneca), current Chairman of ISPE.

PQLI stands for Product Quality Lifecycle Implementation and is ISPE's contribution to the debate on how to implement ICH guidelines Q8 (Pharmaceutical Development), Q9 (Quality Risk Management - QRM), and Q10 (Pharmaceutical Quality Systems).

"The regulators are committed to listening to industry and fostering innovation – and they will," said Morénas. "Regulators recognize that industry is not only global companies. It is the duty of the EU regulators to take into account all kind of companies (medium and small size, generics, etc.)."

Introduction to ICH and the Way ICH Works

Chuck Hoiberg (Pfizer) presented a general overview of ICH and its activities in relation to pharmaceutical development and manufacturing in the three major markets: USA, Europe, and Japan.

ICH has been in existence since 1990 with the following purposes:

- to improve, through harmonization (guidelines), the efficiency of the process for developing and registering new medicinal products in order to make these products available to patients with a minimum of delay
- to reduce or obviate the need to duplicate the testing performed during the research and development of new medicines

Hoiberg outlined the general challenges facing ICH members in development of guidance documents. These include considerable resource requirements both in terms of time commitment and travel costs to attend EWG meetings; differences in tests and procedures in the three regions; and difficulties in obtaining consensus views. However, he asserted that "ICH represents a unique harmonization process which hopefully has a long future ahead."

Overview of the ICH Guidelines

Chris Potter (formerly of Astra Zeneca), presented an overview of the 10 ICH guidelines within the Quality section. He reminded delegates that "if they thought things were difficult and challenging now, they should remember what it was like prior to ICH." While the process is not perfect, it does work.

ICH Q1 to Q7 are technical guidelines and are mandatory for companies selling products within the ICH regions. In contrast, ICH Q8, Q9, and Q10 are about processes and are optional. Potter reviewed each of the technical guidelines in turn, presenting the current status and any outstanding challenges.

He explained the ICH quality vision developed at the Brussels meeting in 2003:

> *"Develop a harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science."*

He also showed the interpretation of this vision from industry's viewpoint:

- a transparent, science and risk assessment approach to dossier submission, review, approval, and post-approval changes
- manufacturers empowered to effect continual improvement throughout the product lifecycle and supply chain
- more efficient and effective regulatory oversight

A challenge the industry currently faces is the different timescales for approval of the same change in different regions. This is difficult to manage by companies that are selling into more than one region.

ICH Implementation Work Groups and ICH Q8/Q9/Q10 Guidelines from an Assessors' Perspective

Jean-Louis Robert discussed some of the new terminology, describing Quality by Design (QbD) as a term which is being used more. QbD is a systematic approach to development, he emphasized. He said he did not want to hear about QbD systems or QbD products. "QbD is not the same as Design Space (DS)," he reminded delegates although DS may well be

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Introduction to ICH: Essential Background to PQLI

an outcome of QbD.

Robert presented the conclusions of an October 2007 ICH report on implementation issues. One of the approaches cited in this report was collaboration with external organizations. The implication here was that these must be not-for-profit organizations and the ISPE PQLI initiative was recognized as an example of this approach.

In the context of regulatory submission, the distinction between large or small molecules is not relevant, said Robert. The key issue is the complexity of the molecule in question.

From the perspective of the Japanese regulators, Yukio Hiyama told delegates they only had two things to do: "conduct good development and write good dossiers." He described the assessment process used in Japan. He emphasised that while Module 3 is very important, the review process starts at Module 2; this is the key document that forms the basis of approval. He confirmed that while the terminology might be different between the Japanese systems and those of Europe or USA, the concepts were the same.

Hiyama emphasized the importance of knowledge flow in both directions between the regulators and industry.

Moheb Nasr, presenting the perspective of the US FDA, told delegates he was looking forward to the PQLI seminar and would use his presentation to overview some of the challenges to be achieved. It is "up to the applicant to design and implement DS," he said. It is not a case of "one size fits all."

Nasr believes there is value in having a formalized way to present QRM data. Some regulators have criticized the example submissions that have been developed, but he did not agree. While accepting that not everything was perfect, he felt it was important to have these tools. For example, he said the FDA is currently using process mapping to analyze risks associated with the Heparin crisis and suggested they might be willing to share the experience with industry once the issue is resolved.

Nasr addressed the question of why there should be an emphasis on Pharmaceutical Quality Systems (PQS) by the assessors. While elements such as tracking and trending of product quality, together with responding to trends before they become a problem, are not necessarily required for submissions, they should form part of the company's PQS.

Nasr said the CMC Pilot Program provided a useful learning curve for both industry and the regulators. He reiterated the comments of Hiyama by saying "good development and good regulatory submissions will elicit better reactions from the regulators."

Robert discussed the European perspective, including the outcome of the March 2008 PAT team meeting in Cork. He told delegates of a growing trend for companies to seek advice from the regulators prior to dossier submission and confirmed that regulators would try to provide the required advice.

Robert emphasized that submissions using either DS or a proven acceptable range are equally valid, but the two approaches should not be mixed together. He confirmed that the Assessors are positive to the new paradigm, and quoted from the European Commission: Variations Public Consultation Paper, issued in October 2007:

> *"Beyond the notion of 'design space,' ICH developments –namely the Q8, Q9, and Q10 guidelines- introduce modern tools (risk management, quality systems) that could facilitate continuous improvement of the manufacture over the products' life cycle, while maintaining a state of control that ensures high standards of quality."*

ICH Implementation Work Groups and ICH Q8/Q9/Q10 Guidelines from an Inspectors' Perspective

For the Inspectors, the European perspective was presented by Jacques Morénas. He highlighted the fact that the new terminology was not yet fully harmonized and understood between regulators and industry or from company to company. There is a requirement for more dialogue between Inspectors, Assessors, and Applicants to make the whole process more transparent. As part of this dialogue, a Q&A page has been established on the EMEA Web site relating to electronic and e-CTD applications.

Morénas said a QRM implementation group has been established by the EMEA, but is not the same as the ICH Q9 Implementation Working Group (IWG). ICH Q9 is an example of QRM is mandatory, he emphasized. While ICH Q9 is not mandatory, the application of QRM is. It has already been formally encapsulated in GMP Part I and is currently being written into GMP Part II. Within the Compilation of Procedures, a new SOP has been developed on the risk-based approach to inspection planning.

With regard to ICH Q10, Morénas said it will probably become Annex 21 of the GMP guidelines within the EU. As such, it is only an example of a PQS, but it is an ideal tool for implementation of ICH Q8 and Q9. There will be no inspection team for ICH Q10 and no certification system, he emphasized. ICH Q10, if used by a company, will be integrated into normal systems and subject to the normal inspection process.

Morénas told delegates they should be prepared to "think globally in order to keep the inspectors happy." "Regulators are happy to be consulted and to support initiative as PQLI as far as it is a global and complementary approach to ICH," he confirmed.

Joe Famulare, described in his introduction as "Mr. GMP," spoke on the FDA Investigators' perspective. He cited the heparin and melamine crises as examples of "critical path" product performance.

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Introduction to ICH: Essential Background to PQLI

Famulare reviewed the challenges relating to ICH Q8, Q9, and Q10 implementation, including Real Time Release (RTR) and process validation issues. If a company implements an RTR process and subsequently has a batch failure, they may not revert to the traditional approach in order to pass the batch, he emphasized.

He discussed the consultation period for ICH Q10, which resulted in more than 300 unique comments from across the three regions. While these were largely supportive, a number of concerns were also expressed in relation to regulatory impact. Famulare told delegates there is a need to communicate the benefits of the new approaches and that would be done by having in place a system that makes the benefits apparent.

In reviewing the FDA's view of Process Analytical Technology (PAT), Famulare said a fundamental tenet of PAT is that "quality cannot be tested into the product; it should be built-in or should be by design." PAT tools can be used to facilitate the implementation of QbD and PAT is more than just an analyzer, he emphasized.

The issue of training, both for Assessors and Investigators, is recognized as a key challenge and this process was started by the PAT cadre within the FDA, even before the advent of ICH Q8, Q9 and Q10.

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PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2008, Vol. 28 No. 3

International

The PIC/S[1] Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments (PE 010-2) has been revised in order to correct a misprint in Annex 1.

Australia

The Australian Therapeutic Goods Administration (TGA) has issued via their Web site[2] draft documents for consultation on General Requirements for Tablets and Capsules[3] and on Microbiological Standards for Medicines.[4] The draft guidance on General Requirements for Tablets and Capsules outlines standards for the dosage forms with reference to National Pharmacopoeia (for example, to dissolution tests according to BP, PhEur or USPNF should be performed) and provides an extensive 'Q & A' section explaining which standard should be applied for any particular solid dosage formulation.

The draft guidance on Microbiological Standards for Medicines contains the proposals and provides an extensive 'Q & A' section providing examples of the standards to be applied and dosage forms for which consideration is required.

The TGA has also announced[5] that they are developing a consolidated reference document detailing the Australian regulatory requirements for medical devices. The document will provide guidance on all the regulatory requirements for medical devices. As each section is prepared, it will be released for comment on the technical aspects of the document and each completed section will also be available as it is finalized. However existing guidance will effective until it can be fully replaced.

The new guidance will be available in full on the TGA Web site by the end of the calendar year (2008), the intended completion date of the project.

The TGA has also announced the adoption of the following EU guidelines, effective from February 2008:

- EMEA/CHMP/BWP/298388/05 – Guideline on Validation of Immunoassay for the Detection of Antibody to Human Immunodeficiency Virus (Anti-HIV) in Plasma Pools
- EMEA/CHMP/BWP/298390/2005 – Guideline on Validation of Immunoassay for the Detection of Hepatitis B Virus Surface Antigen (HBSAG) in Plasma Pools.

Canada

In March 2008, Health Canada[6] released the following Step 2 ICH Guidelines for public consultation and comment with 60 days:

- Q4B Annex 2: Test for Extractable Volume of Parenteral Preparations General Chapter (EMEA/CHMP/ICH/559409/2007)
- Q4B Annex 3: Test for Particulate Contamination: Sub-Visible Particles General Chapter (EMEA/CHMP/ICH/561176/2007)
- Q8 Annex: Pharmaceutical Development (EMEA/CHMP/ICH/518819/2007)

Egypt

Products to be registered in Egypt are subject to new stability data requirements.[7] Previously, a stability study had to be submitted following analysis of registration samples which may be from small scale development batches and this was the only stability study requirement. However, the new system requires a similar study as a first step but further data from a representative production batch must be submitted. For shelf life extensions, yet another real time study is required. Thus, the new rules are broadly aligned with international standards requiring real-time stability data on production batches using large-scale industrial equipment. They also ensure product quality as manufacture of the first production batch is monitored by an inspector.

The requirements are not expected to create any additional burden on large, well-established companies. However, as production lines must be ready before any products can be approved, it is intended that companies attempting to register multiple products without having the capacity to produce them, especially with purchased stability data, will be excluded.

Europe

In February 2008, The European Commission DG Enterprise and Industry released via their Web site[8] updated GMP guidelines Volume 4 to implement the concept of Quality Risk Management. With the revision of GMP Part I, Chapter 1 on Quality Management quality risk management has become an integral part of a manufacturer's quality system, and will also be considered in a future revision of GMP Part II. However, the ICH Q9 guideline as such has been implemented with a new Annex 20 to provide an inventory of internationally acknowledged risk management methods and tools together with a list of potential applications.

Further, a revision to Annex 1 entitled Manufacture of Sterile Medicinal Products has now been made public. The revision of the Annex was necessary to align the classification table for environmental cleanliness of clean rooms with ISO standards and provides supplementary guidance on the application of the principles and guidelines of GMP to sterile medicinal products. The guidance has been updated in four main areas:

- Classification table for environmental cleanliness of clean rooms, and associated text
- Guidance on media simulations
- Guidance on bioburden monitoring
- Guidance on capping of freeze-dried vials

The new annex should be implemented by March 2009 except for the provisions on capping of freeze-dried vials, which should be implemented by March 2010. In March 2008, the outcome of the public consultation on a draft report on specific provisions applicable to traditional herbal medicinal products was published.

The European Medicines Agency (EMEA) has written to all Marketing Authorisation Holders requesting on assessment of the risk of occurrence of contamination with mesilate esters and related compounds in medicinal products[9]. This risk assessment should also include the cleaning procedures and the used solvents. If the outcome of the risk assessment is that the risk is not satisfactorily controlled taking into account the requirements of the Guideline on

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the limits of genotoxicity impurities (EMEA/CHMP/QWP/251334/2006), a variation should be submitted with the appropriate amendments to the manufacturing process and/or control of active substance and/or finished product.

The Committee for Medicinal Products for Human Use (CHMP) [10] has published reports from its February and March plenary meetings held on 18 to 21 February and 17 to 19 March 2008, respectively.

The following relevant guideline[11] has been adopted for consultation by the Biologics Working Party:

- Concept paper on a guideline on the chemical and pharmaceutical quality documentation concerning biological investigational medicinal products in clinical trials(EMEA/CHMP/BWP/ 466097/2007).

The following relevant guidelines[11] have been prepared or adopted for consultation by the Quality Working Party:

- Reflection Paper on Water for Injection Prepared by Reverse Osmosis (EMEA/CHMP/CVMP/QWP/28271/2008). This reflection paper aims to stimulate discussion by arguing against the acceptability of using reverse osmosis for the production of water for injections.
- Question-and-answer document on Glycerol (Glycerin) contamination (EMEA/CHMP/CVMP/QWP/76509/2008).
- Guideline on the Specification Limits for Residues of Metal Catalysts of Metal Reagents (EMEA/CHMP/SWP/QWP/4446/2000)

The Committee on Herbal Medicinal Products (HMPC)[12] has published their monthly meeting report[7] for the meeting held on 5 to 6 March 2008.

The committee reports that at a meeting of the Quality DG held in February, the HMPC adopted a work plan including the drafting of additional guidance documents on stability testing for herbal products and on comparability of herbal substances/preparations (e.g. extracts using different solvents).

The Paediatric Committee (PDCO)[13] has published their monthly meeting reports for the meetings held on 13 to 15 February and 12 to 14 March 2008. No new relevant information was noted.

The Committee for Orphan Medicinal Products (COMP)[14] has published their monthly meeting reports for the meetings held on 5 February 2008. No new relevant information was noted.

The Committee for Veterinary Medicinal Products (CVMP)[15] has published their Monthly Reports of Application Procedures, Guidelines and Related Documents for February and March 2008. Each includes an accumulative summary of the opinions issued by the CVMP in the current year and a list of adopted Guidelines and other public documents.

Noteworthy, the following relevant guidelines were adopted for public consultation at their February meeting:[16]

- Reflection Paper on Water for Injection Prepared by Reverse Osmosis (EMEA/CHMP/CVMP/QWP/28271/2008, as above).
- VICH guideline (GL45) on Quality: Bracketing and Matrixing Designs for Drug Substances and Medicinal Products (EMEA/CVMP/VICH/581467/2007) was adopted for public consultation until August 2008. This guideline addresses recommendations on the application of bracketing and matrixing to stability studies conducted in accordance with principles outlined in the VICH GL 3 (R) on stability testing.

Gulf States (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE, and Yemen)

Generics companies seeking to register their products centrally in the Gulf States are subject to mandatory new requirements[17] relating to the submission of stability studies and of active ingredient information. The centralised registration procedure allows companies in Gulf Co-operation Council member states to submit a single registration rather than registering separately in each country. The rules state that registration files from generics manufacturers will not be accepted unless they include stability studies covering the complete shelf-life period from mid 2007 to the date of registration. Studies submitted with the registration must meet the approved storage temperature and humidity of 30 degrees Celsius and 65%RH, respectively. Applicants that have already submitted preparations for registration have a three-month grace period for providing this information.

Registration files need to identify also the source of active pharmaceutical ingredients for preparations approved by authorities in other countries and the certificate of suitability. Applicants may not include more than two raw material sources and should inform the committee of any future changes.

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This information was provided by Ian Morland, MRPharmS, PhD, Pharmaceutical Research Associates (UK).

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PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2008, Vol. 28 No. 3

Regulators and Industry Discuss PQLI in Copenhagen

by Dr. Kate E. McCormick, ISPE European Education Advisor

During the ISPE European Congress on Innovation 7 – 11 April in Copenhagen, regulators joined industry for several days of highly interactive seminars and workshops on the ISPE Product Quality Lifecyle Implementation (PQLI) initiative.

Approximately 90 participants continued the global discussion on PQLI, an industry-driven effort encouraged by the US FDA and led by ISPE, to find practical, global approaches to implementing the high level ICH Guidelines Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), and Q10 (Pharmaceutical Quality Systems).

The following are key messages and highlights from the PQLI sessions, held 10 – 11 April:

The Future Role of Pharmacopoeias

Susanne Keitel of the European Directorate for the Quality of Medicines and Healthcare (EDQM) within the Council of Europe addressed the question of the future role of pharmacopoeias. She started with an overview of the objectives of a pharmacopoeia, which are to:

- Provide authoritative quality standards for the medicinal substances that are important for public health.
- Respond rapidly to new risks to public health (new impurities, TSE, counterfeit medicines etc.).
- Facilitate the free movement and trade of medicines among countries.
- Facilitate access to high-quality medicines, by allowing free movement.

Keitel confirmed that these objectives hold true for all three ICH regions.

She also confirmed that the European Directive 2003/63/EC makes provision for revision of monographs when required. She emphasised there is a need for a flexible and creative approach to revision to make sure people get what they want, but it can happen.

Keitel addressed the challenges presented by ICH Q8, Q9, and Q10. She said she believes there is hesitancy within industry to share detailed information with regulators and she is currently unsure whether this approach will be adopted by all companies in the future.

On the subject of Real-Time Release (RTR), she confirmed this can be adopted by companies if appropriate, since the European Pharmacopoeia (Ph. Eur), while legally binding, allows for alternative approaches. However, she emphasised the need to comply throughout shelf-life and hence there is a need for validation compliance.

In conclusion, Keitel confirmed that EDQM and Ph. Eur are committed to strive for harmonized standards and are very positive about the new concepts. However, she emphasised that whatever approach is taken by a company, safeguarding public health should be the first priority.

Establishing Release Specification – Current and Future

This session was a joint regulator/industry presentation on establishing release specifications. For the regulators, Jean-Louis Robert of the National de Santé in Luxembourg started by reminding the delegates of ICH Q6A/B on specifications and emphasised that a specification is perceived as a reflection of the quality of a product. However, it is not a guarantee since it is only one of a number of key elements. He went on to review the history of pharmaceutical development over the past decade and stated that PAT was originally defined as a valid approach by FDA, then was later taken up by ICH.

Robert pointed out that PAT tools are part of the control strategy; they are not a system. He said that ICH Q8 is nothing new since it has always been the case that quality comes from development. "There may be a new paradigm, but it is not necessarily a revolution," he said. "RTR is not necessarily the target for all companies." To have a better process for development and more understanding of product and process also will be beneficial.

Robert concluded by reminding the delegates that it is not up to the regulators and assessors to tell manufacturers what to do. It is up to the manufacturer to develop a product fit for use. It is up to the assessor to evaluate if the product is suitable for its intended purpose.

In the industry response, Mike James of GlaxoSmithKline said the FDA document, Pharmaceutical cGMPS for the 21st Century – A Risked Based Approach, generated useful discussion which then lead to specific ICH projects. He suggested that there may be a need to generate a new definition for specifications in the future, based on QbD, but now is not the right time to do this.

James said Q8R provides very useful guidance for setting release specifications. In its current form, it does what it needs to and hopefully it won't be changed too much during

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the remainder of the ICH process. The annex provides a good summary of differences between the current minimal approach and the proposed enhanced approach using QbD. However, he reiterated the point made by previous speakers that the enhanced QbD approach is optional.

James said the question of whether industry believe the regulatory door is open wide enough would be discussed during the workshops. However, he believes that the enhanced approach is feasible and knows two to three companies already doing it.

The Qualified Person

There was a presentation that dealt with the topic of the Qualified Person (QP), a concept unique to Europe within the ICH regions at present. Françoise Robinet from Novartis started with a reminder of the current EU legislation on QPs and said this legislation had been interpreted differently in different Member States. The situation is further complicated by manufacturing processes that stretch across a number of sites within both EU and non-EU countries.

Robinet addressed the question of "who is in control?" If the QP responsible for the release has to rely on a chain of other QPs often spanning several countries, the situation requires meticulous organization through specific delegation and/or contracts and audits. There is a great danger that "everybody's responsibility becomes nobody's responsibility." She described how the requirements are addressed within one model, that of the French Responsible Pharmacist.

Robinet concluded there is room for improvement in harmonizing the role and responsibility of the QP across the EU. She said this is becoming crucial with the enlarged EU and reminded delegates that the final objective is to ensure quality and safety not only for the patients, but also for industry.

In response, Jacques Morénas, Associate Director of the Inspectorate and Companies Department of the French regulatory agency Afssaps and Chair of PIC/S, presented diagrammatically the responsibilities of the QP in the 1970s when the role was first established; monitoring of a simple linear process from incoming materials to distribution. Today's equivalent also was shown diagrammatically and it reiterated Robinet's assertion that the situation is much more complex now.

Morénas reminded delegates that while QbD, QRM, and PQS are mandatory; ICH Q8, Q9, and Q10 are only possible frameworks.

In conclusion, Morénas said that PQLI does not currently include considerations of certification and batch release. He said it may be necessary to simplify PQLI and integrate the role of the QP before being able to sell it to all EU regulators. He emphasized that the "QP cannot be superman or superwoman." He confirmed that "EU regulators are ready to work with ISPE on this topic, taking into account it is a critical point. Work is already in progress as we can see with work made by the PAT team at the EMEA level and we will be happy to continue."

Workshop on Design Space (DS)

This workshop concentrated on APIs in one session and on drug product in another session. Identified barriers to building a design space included: high resource requirement, relative to the traditional approach; high investment requirements and uncertainty over capability of third party suppliers. While incremental investment of FTE and time is relatively small, incremental investment of mental energy (how that investment is placed) is larger.

In terms of training, it was felt that a roadmap approach would be more appropriate than a checklist. There will be a requirement for delivery of training and possibly tools in multivariate process design principles across many disciplines. This was seen as a possible opportunity for ISPE. Issues were identified around understanding of the "science of scale" and the application of prior knowledge.

From the perspective of the regulators, they have seen very few DS applications. As the number of applications increases, the system will be tested and interaction with the regulators will develop.

Workshop on Criticality

Definition of criticality was recognized as difficult. The use of Decision Trees (DTs) may be useful, but will not always be appropriate. They are better for process variables and Critical Process Parameters (CPPs) than for Critical Quality Attributes (CQAs).

There is a need for common terminology and integration of all the concepts within a single case study. In discussing how criticality can be managed, a resonating theme from both sessions was that criticality should be based on QRM.

There were some conclusions drawn regarding critical parameters, non-critical parameters, and intermediate ones, defined as "X". The need to link in with quality systems was acknowledged.

Final comments included:

- Criticality is useful for Marketing Authorizations.
- QRM is fundamental to criticality.
- Industry would like to reduce the number of variables.

Workshop on Control Strategy (CS)

This workshop was seen as an opportunity to present a consistent approach to the regulators and also to progress understanding of the model and control strategy. It was an attempt to encourage dialogue and reduce the conservatism of industry.

Positive comments relating to the model included the fact that it is a systematic approach which links CQAs to manu-

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facturing controls. It was agreed that while GMPs and PQS serve as the foundation of the model, they should not be included in Level 3.

Areas for future development included the relationship to PQS, role of QP, continuous monitoring, triggers for review and continuous improvement, whether of product, process or CS.

"This workshop was seen as an opportunity to present a consistent approach to the regulators and also to progress understanding of the model and control strategy."

It was emphasized that the Task Team should try not to introduce new terminology that is confusing. They must go back and confirm that they are consistent with definitions given by ICH.

The model also must be applicable to large molecules although most work is currently being done on small molecules. There is a need for an integrated model, as a more comprehensive example, e.g., submission presentation or mock P5.

From the regulators' perspective, it was emphasised that the definition of control strategy in ICH Q10 is designed to cover both minimal and enhanced approaches. They also felt that the real world is more complex than the simple examples used to demonstrate the model.

Workshop on Legacy Products (LP)

As LP is new to PQLI, this was the first public discussion of this topic; attendees were contributing to the start of the process. During discussions, it was agreed by some people from industry and regulators from all three regions that ICH Q8 is also applicable to legacy products (although not all companies agree).

There would be benefits in reduction of post-approval submissions for low value legacy products. These would include business benefits since there is more certainty about the product and the market. The company would know what flexibility is required and there would be existing data available for review. The molecule is not at risk since it is already on market; hence, it would be known that there would be some return to the investment.

Requirement for implementation would include more consistency since currently definitions of deviations vary with companies. There needs to be a common glossary of terms and the company's PQS must be able to manage both paradigms.

Roundtable Discussion on Role of the Qualified Person

This roundtable was cancelled due to lack of attendees. This was probably due to the nature of the delegates attending the seminar. A show of hands suggested fewer than 10 QPs attending the seminar in total. However, the opportunity was taken for the moderators to review the topic with the regulators in attendance.

It was concluded that the QP issue is a regional one. It is not a key issue within the context of ICH, but is critical from the European perspective. It is known that the legislation is interpreted differently across the Member States and it was felt that it would be useful to gain an overview of exactly what is happening across the EU both at a country and a company level.

With the implementation of ICH Q8, Q9, and Q10, the role of the QP will be essentially unchanged. However, the QP needs to ensure his/her understanding and knowledge of the new approaches, tools, and techniques are adequate to certify batches. The regulators confirmed that the QP need not personally be the expert in all these areas, but needs enough background to know what systems and processes are in place, who to ask, what to ask, and how to use this in decision making to satisfy.

Outside of EU, there is a growing uptake of PIC/S GMP and other countries are starting to show an interest in the QP role. It was agreed that industry interested parties (such as Efpia, EGA, QP Association, ISPE, PDA) would request a dialogue with EU regulators to explore the future role of QP, including consideration of possible revisions of guidance documents.

Roundtable Discussion on Real Time Release (RTR)

It was concluded that regulators are not a hurdle to implementation of RTR since the door is open and RTR is widely accepted by more agencies. However, a cultural change still needs to occur in industry. There are some success stories out there, but they need to be turned into case studies that can be used to guide other companies.

While it makes sense from a scientific point of view to apply RTR to all products, it needs to be reviewed from a business case perspective. Different categories might be treated differently (e.g., high volume products, problematic products, continuous manufacture).

Data collection and storage was seen as a significant challenge. In practice, data should only be collected if there is a clear purpose and use. In terms of handling atypical results, deviation scenarios and their management should be prepared prior to submission. Returning to the traditional methods of release in the case of a RTR failure is not an option.

There needs to be an increase in the competency and skill set between R&D and manufacturing. Understanding is needed throughout the organization at all levels. More training in statistics, mathematical tools, and chemometrics is required. Risk assessment should be carried out by multidisciplinary teams.

Concludes on page 5.

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Thoughts of a Retired GAMP Editor

by Tony Margetts, AstraZeneca (retired)

I have been asked to write down a few thoughts on retiring from the ISPE/GAMP Editorial Board after close involvement with most of the GAMP guidance documents.

Through ISPE, I have made many friends and have many happy memories of people, places, and events scattered throughout the world during the last 20 years.

I have penned a number of thoughts and some key people who helped to develop the ideas which have recently culminated in the publication of GAMP 5.

I became involved in developing industry guidance after a meeting of the UK Medicines Control Agency (MCA) at Keele, England in 1989, where I first met Tony Trill (UK Medicines Inspector with special responsibility for computer systems validation).

At this time, Mike Bennoson asked me to write a monograph for the Pharmaceutical Industry Group of the Institute of Quality Assurance in the UK. Early thoughts on the subject were greatly helped by my close colleague Pat Jeater of Zeneca Pharmaceuticals.

I became more involved in the aftermath of an FDA inspection of two UK companies by Ron Tetzlaff in 1991, which for the very first time had raised a number of issues related to Computer Systems Validation.

Ron called these systems 'automated' – this is the origin of the A in GAMP.

I later had a particularly useful meeting with Ron Tetzlaff and Sam Clark (US FDA) during my first ISPE meeting in Zurich in 1992.

I received telephone calls from David Selby of Glaxo Manufacturing Services and Clive Tayler of the Wellcome Foundation, both of whom also were considering how to react to these observations by Ron Tetzlaff.

This contact resulted in the formation of an industry working group initially called the Pharmaceutical Industry Computer Validation (PICSV) Forum. The Forum aimed to develop guidance in this area.

Initially, there were just four active members of the Forum, namely David Selby, Clive Tayler, Annis Bratt, and me. We had a great deal of success in raising the profile of computer validation both in the UK and in Europe.

During this period, I first met Paul D'Eramo (US FDA) at a conference in Athens, Georgia, US and we found that we had a lot of common ideas on the subject of computer validation.

The initial PICSV Forum draft document was based on an existing Zeneca Pharmaceuticals document called Validation Management (VMAN). The PICSV Forum developed the VMAN document through a number of draft versions, culminating in the First Draft, which was launched at the Queen Elizabeth Conference Centre in London, England in March 1994. This First Draft was distributed to obtain consultation, particularly from suppliers of automated systems.

I remember Chris Derrett (now Chair of the Facilities TDSC) intercepting me to say that the guidance was all very good, but there was no mention of process control systems - we developed this approach in later versions, for which John Andrews (KMI/PARAXEL) was a great help.

By this time, key members of the team included Tony Trill, Rob Almond (Glaxo Wellcome Operations), and Terry Lucy (Wellcome Foundation). The term GAMP (Good Automated Manufacturing Practice), was coined by Tony Trill, while Rob and Terry developed the GAMP categories idea. Other colleagues, Bob Paige (Eutech) developed our approach to testing and Mike Senior (Zeneca Pharmaceuticals) developed our approach to code review; both of these topics were particular problems at the time.

The Second Draft called "GAMP Guidance for Suppliers" was made available in January 1995 and saw the first bond between ISPE and the GAMP Forum with ISPE providing support for production of the Second Draft.

Version 1.0 of the GAMP Guide was launched in March 1995 in Amsterdam, Holland.

During 1995, we began to develop links within Europe through the Inter-

What Would GAMP be Without Dr. Tony Margetts

by David Selby, Selby Hope International Ltd.

I think it is true to sat that without Tony, there would never have been any GAMP guidance.

In the early days when we were deciding what to do, Tony agreed to lead the team that produced the first Pharmaceutical Industry Computer System Validation Forum (PICSV) Guide, which later became GAMP. He introduced the first version of the "V" model to the team and also invited in Tony Trill from the UK Regulatory Agency to join. Both initiatives paid off handsomely.

In later years, Tony Margetts led the GAMP Editorial Team and his project management skill always ensured that the various GAMP versions were delivered on time in a consistent style to an increasingly high standard. GAMP 5 is his crowning glory.

His contribution to ISPE and to the GAMP project, in particular, is immeasurable. The industry owes him a great debt of gratitude.

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ENGINEERING PHARMACEUTICAL INNOVATION

Thoughts of a Retired GAMP Editor

national Association for Pharmaceutical Technology (APV) and the VDI/VDE Society of Measurement and Automation (GMA) / Standardization Association for Measurement and Control in Process Industries (NAMUR).

I still remember our first meeting in the Hague with Bob Best when we agreed to become involved with ISPE; this has proved to be a highly beneficial relationship for all concerned.

Ken Chapman invited me to the US in 1994 to present to the Pharmaceutical Manufacturers Association (PMA). We continued to develop our US contacts and ISPE/PDA had a large meeting with 300 attendees in Baltimore in 1996. I recall talking to a US supplier who said that GAMP was the first useful guidance to actually tell suppliers what they needed to know in order to supply to pharmaceutical industry customers. Ken Chapman was a big champion of GAMP.

GAMP became thicker and thicker with more content. GAMP 3 (the back to front version, including case studies) was launched in Amsterdam in 1998 and later GAMP 4 with even more content was launched in Amsterdam in 2001 and Washington in 2002.

GAMP Americas was formed in 2000 and as these groups also developed Guidance, Randy Perez joined the Editorial Board to provide a link between Europe and the US.

As the GAMP Forum grew, and several special interest groups developed guidance, it was felt that a group was needed to coordinate and manage these publications. We developed an Editorial team, mainly Sion Wyn, Colin Jones, Gail Evans, and myself, as Chair, together with invited participants to develop content for the new documents. North Wales, UK, and the wonderful Conway Valley featured strongly in our editing sessions, GAMP 4, GAMP Good Practice Guides on electronic records and signatures, and on infrastructure were edited there and a lot of GAMP 5 was created there.

In the period 2001 to 2006, I was busy with GAMP training which took me to many US cities, India, Australia, China, and Japan. I had many visits to Japan with work and sometimes was able to combine these with some GAMP work. I remember an invitation to GAMP Japan in 2005 where I had a particular welcome, and I also had further welcoming experiences in India and Australia.

I have been asked on a number of occasions if this validation work uncovers any real problems; well the answer is usually 'yes.' Validation does uncover possible future problems. One particular instance I remember was when we discovered that the clock on the control system of a sterilization autoclave was incorrect, which could have resulted in non-sterile product.

I would like to give my thanks to all my many friends in ISPE who have

Concludes on page 6.

Regulators and Industry Discuss PQLI in Copenhagen

Continued from page 3.

Roundtable Discussion on Submission vs. Inspection

The regulators believe this is not a big issue in Europe and Japan (and even US). However, although some of the industry people agreed, this was not a unanimous view.

Some questions that were raised included:

- Can the assessor/inspectors interaction learn from tech transfer between R&D and manufacturing?
- Should there be a presubmission dialogue between Assessors, Inspectors, and Applicants to identify where data should go?

Skill is needed to write the dossier in an appropriate way, without pages of data. DS definition is an issue for the assessors. Control strategy may be an issue for both Assessors and Inspectors.

It was concluded that this is a regulator's issue. It is up to them what goes into the dossiers, even though industry decides how it is interpreted. Therefore, it is proposed that this topic be considered within the ICH IWG. It is not an issue for ISPE to take further.

Learn More About PQLI

For additional reporting from the PQLI sessions held in Copenhagen, visit www.ISPE.org/pharmaceuticalengineering to read the ISPE Update On-Line Exclusive, **Introduction to ICH: Essential Background to PQLI,** by Dr. Kate E. McCormick, ISPE Education Advisor.

For additional resources on PQLI, including Copenhagen Congress presentations available for download, visit www.ISPE.org.

Editor's Note: The June issue of ISPE's *Journal of Pharmaceutical Innovation* will feature five papers focusing on PQLI, including an overview, design space, criticality, and control strategy.

To access the June issue, visit www.ISPE.org/jpi.

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ENGINEERING PHARMACEUTICAL INNOVATION ISPE

Mark Your Calendar with these ISPE Events

June 2008

2 – 3	**ISPE Singapore Conference in association with INTERPHEX *ASIA* 2008, Suntec, Singapore**
2 – 5	**ISPE 2008 Engineering Regulatory Compliance Conference, Leading-edge seminars review the latest regulatory perspectives and hot topics: Commissioning and Qualification, Containment Technologies, HVAC, Critical Utilities, Risk-MaPP, Barrier Isolation, Facilities, MES, Cleaning, and much more, Crystal Gateway Marriott, Arlington, Virginia, USA**
4 – 5	Spain Affiliate, Conference on GAMP® 5, TBD, Spain
5	UK Affiliate - Central Region, Event, Diamond Project Visit, Harwell, Oxfordshire, United Kingdom
12	Chesapeake Bay Area, 2008 Summer Social, Baltimore Inner Harbor Cruise aboard the Black Eyed Susan, a unique paddlewheel riverboat, Baltimore, Maryland, USA
12	Italy Affiliate, Conference on Manufacturing and Control Systems Security, Rimini, Italy
13	Puerto Rico Chapter, Site Tour and Training, Project Management and Technical Writing – Project Management and Key Success Factors, Mayaguez, Puerto Rico, USA
14	Carolina-South Atlantic Chapter, Student Event: Susan G. Koman Breast Cancer Walk, Meredith College, Raleigh, North Carolina, USA
17	Boston Area Chapter, Seminar, Topic on "Facility Monitoring System Validation," The Royal Sonesta Cambridge, Cambridge, Massachusetts, USA
18	New Jersey Chapter, Chapter Day, Holiday Inn, Somerset, New Jersey, USA
19	Rocky Mountain Chapter, Spring Dinner Meeting, Millennium Harvest House Hotel, Boulder, Colorado, USA
19	South Central Chapter, Golf Tournament and Awards Banquet, Sky Creek Ranch Golf Club, Keller, Texas, USA
20	New England Chapter, Third Annual Family Night at the ballpark with barbeque, fireworks and Connecticut Defenders Baseball, Dodd Stadium, Norwich, Connecticut, USA
23	Argentina Affiliate, Workshop Topics included: Quality Systems Standard ISO 17025 to Develop and Establish a Quality System in the Laboratory, Laboratorios Rontag Auditorium, Buenos Aires, Argentina
25	Brazil Affiliate, One-Day Event on Process Validation – Current Approach, Mercure Apartments, Sao Paulo, Brazil
26	Midwest Chapter Golf Outing, St. Louis, Missouri, USA
30	Brazil Affiliate, One-Day Event on Calibration Management, Windsor Florida Hotel, Rio De Janeiro, Brazil

July 2008

3	Italy Affiliate, Night Event, Milan, Italy
9	UK Affiliate - Northwest Region, Seminar on "Application of Lean and Six Sigma Techniques," Siemens Manufacturing Facility, Congleton, United Kingdom
15	San Francisco/Bay Area Chapter, Commuter Conference on "Design Trends – Manufacturing Control Systems, Process Systems, New Technologies, and Disposables," Genentech, South San Francisco, California, USA
17	Pacific Northwest Chapter, UW School of Medicine Tour, Seattle, Washington, USA
17	Puerto Rico Chapter, Program on "Lyophilization," Guaynabo, Puerto Rico, USA
21	Argentina Affiliate, Workshop on "Risk Management in the Microbiology Laboratory," Laboratorios Rontag Auditorium, Buenos Aires, Argentina
21 – 22	2008 India Conference, "Quality Risk Management," Mumbai, India
22	Brazil Affiliate, One-Day Event on Revestiment, Sao Paulo, Brazil
31	Carolina-South Atlantic Chapter, Durham Bulls Family Night, Durham, North Carolina, USA
31	San Francisco/Bay Area Chapter, Fun Day with Networking Breakfast, choose between Golf Tournament or Napa Winery Tours, Chardonnay Golf Club, American Canyon, California, USA

Dates and Topics are subject to change.

...Retired GAMP Editor

Continued from page 5.

helped with all the document development. I hope these documents continue to develop and provide industry with practical guidance.

Learn More About GAMP 5

The GAMP 5 European Launch Conference held in Copenhagen in April, opened to a record breaking audience of almost 400 attendees – the largest single audience ever for this type of ISPE event. Visit www.ISPE.org/pharmaceuticalengineeering to read the ISPE Update On-line Exclusive, **GAMP 5 Debuts to a Record Breaking European Audience,** by Gail Evans, ISPE Technical Documents Writer/Editor.

Ruff and Ang Awarded CPIP Credentials

Certified Pharmaceutical Industry Professional (CPIP) credentials were awarded in April to Michael Ruff, CPIP, Vice President Pharmaceutical Development, Metrics Inc., USA, and Ting Siong Ang, CPIP, Quality Assurance Manager, Aventis Pharma Manufacturing Pte, Ltd., Singapore.

The CPIP credential, conferred by the ISPE Professional Certification Commission, offers the first competency-based international certification for pharmaceutical professionals and covers a range of competencies from drug product development through manufacturing. Professionals are assessed through demonstrated education, industry experience, and a rigorous examination.

The certification offers enhanced credibility, peer respect and recognition, and greater opportunities for professional advancement.

To learn more and obtain a CPIP eligibility application (free download), visit www.ISPE-pcc.org.

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PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2008, Vol. 28 No. 3

Architects, Engineers – Constructors

CRB Consulting Engineers, 7410 N.W. Tiffany Springs Pkwy., Suite 100, Kansas City, MO 64153. (816) 880-9800. See our ad in this issue.

IPS – Integrated Project Services, 2001 Joshua Rd., Lafayette Hill, PA 19444. (610) 828-4090. See our ad in this issue.

Parsons, 150 Federal St., Boston, MA 02110. (617)-946-9400. See our ad in this issue.

Bioreactors/Fermenters

Cleanroom Products/Services

AdvanceTec, 485 Southlake Blvd., Southport Corporate Center, Richmond, VA 23236. (804) 378-1550. See our ad in this issue.

AES Clean Technology, 422 Stump Rd., Montgomeryville, PA 18936. (215) 393-6810. See our ad in this issue.

Dagard USA Corp., 1251 Avenue of the Americas, 34th Floor, New York, NY 10020. (212) 583-4928. See our ad in this issue.

Employment Search Firms

Jim Crumpley & Associates, 1200 E. Woodhurst Dr., Bldg. B-400, Springfield, MO 65804. (417) 882-7555. See our ad in this issue.

Filtration Products

Siemens Water Technologies, 10 Technology Dr., Lowell, MA 01851. (978) 934-9349. See our ad in this issue.

Instrumentation

Hach Ultra Analytics, 5600 Lindbergh Dr., Loveland, CO 80539. (970) 663-1377. See our ad in this issue.

Label Removal Equipment

Hurst Corp., Box 737, Devon, PA 19333. (610) 687-2404. See our ad in this issue.

Passivation and Contract Cleaning Services

Active Chemical Corp., 4520 Old Lincoln Hwy., Oakford, PA 19053. (215) 676-1111. See our ad in this issue.

Astro Pak Corp., 270 E. Baker St., Suite 100, Costa Mesa, CA 92626. (800) 743-5444. See our ad in this issue.

Cal-Chem Corp., 2102 Merced Ave., South El Monte, CA 91733. (800) 444-6786. See our ad in this issue.

Spray Dryers

GEA Niro Pharma Systems, 9165 Rumsey Rd., Columbia, MD 21045. See our ad in this issue.

Sterile Products Manufacturing

Tanks/Vessels

Eagle Stainless, 816 Nina Way, Warminster, PA 18974. (215) 957-9333. See our ad in this issue.

Used Machinery

Validation Services

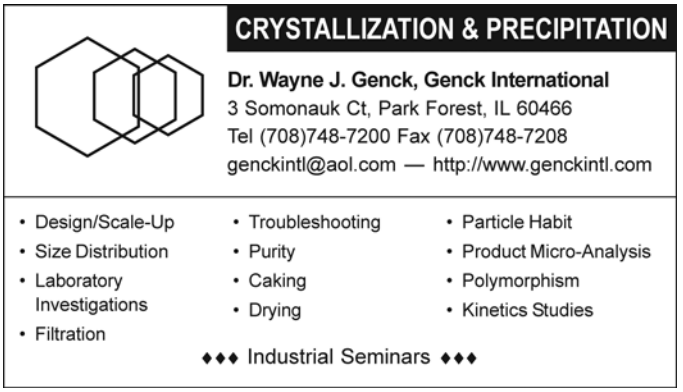
Commissioning Agents, Inc., 1515 N. Girls School Rd., Indianapolis, IN 46214. (317) 710-1530. See our ad in this issue.

ProPharma Group, 10975 Benson Dr., Suite 330, Overland Park, KS 66210; 5235 Westview Dr., Suite 100, Frederick, MD 21703. (888) 242-0559. See our ad in this issue.

Water Treatment

Siemens Water Technologies, 10 Technology Dr., Lowell, MA 01851. (978) 934-9349. See our ad in this issue.

Veolia Water Solutions & Technologies, Global Headquarters, L'Aquarène – 1, place Montgolfier, 94417 Saint-Maurice Cedex, France, www.pharma.veoliawaterst.com, Email: pharma-info@veoliawater.com. See our ad in this issue.



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