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Speeding Up Formulation Development

Ronald D. Snee

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QbD principles and strategic thinking can reduce the time required to optimize formulation.

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To help pharmaceutical and biotech companies improve their operations, FDA has been promoting the use of quality by design (QbD) (1, 2). Much has been written about the QbD concept of a "design space" from a manufacturing process perspective. Little has been published, however, about using QbD in formulation development, including the development of formulation design spaces.

Formulation studies typically involve the optimization of multiple ingredients including the API, lubricants, binders, and disintegrants. Such optimization is a difficult challenge when a large number of components are involved, which is typically the case.

An additional challenge is that, in many formulations, the amounts of components in the formulation must add up to 100% or some fixed amount. A pharmaceutical formulation, for example, might consist of: 15% API, 35% lactose, 45% microcrystalline cellulose (MCC), 4% Starch, and 1% magnesium stearate. The percentages of the ingredients add up to 100%; thus, when levels of one or more components are changed (i.e., increased or decreased), the percentages of one or more of the remaining components must be changed (i.e., decreased or increased by a corresponding amount).

The statistical design-of-experiments approach, DoE, which is at the core of QbD, has the flexibility to deal with multiple components that involve constraints of many different types. In the statistical approach, a series of formulations is created and tested in a planned sequence. The levels of the candidate components are varied in a blending design and the performance of the formulations is measured. A model is fit to the data and critical components, and then blending characteristics are identified.

Response surface contours are examined graphically and analytically to determine the design space, the region of the best values of the response that meet specifications. Additional confirmatory formulations are typically tested to verify the model predictions. The statistical approach has many important benefits, as discussed by Montgomery (3), Snee and Hoerl (4), and many others. As a result, formulation understanding is greatly increased as well as the prob-

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Table I: Phases of formulation development experimentation.

Characteristic	Screening phase	Optimization phase
No. of components	More than 6	2–5
Desired information	Critical components	Prediction equation, optimization, design space
Model form	Linear blending	Linear and curvilinear blending
Experiment design	**Screening:** Simplex and extreme vertices designs	**Response surface:** Simplex and extreme vertices designs

Table II: Pharmaceutical tablet compactability study – component ranges (%).

Component	Low level	High level
X1=Microcel	50	88
X2=KollydonVA64	10	25
X3=Flowlac	0	25
X4=KollydonCL30	0	10
X5=PEG 400	0	10
X6=Aerosil	0	3
X7=MgSt	**0.5**	**2.5**

ability of successful formulation development (4–7). This article discusses some of the issues involved, and outlines a strategy for dealing with them. To clarify abbreviations in the text, MCC refers to Avicel PH105; CP is Hiviswako 104; and PVP is Providone K90.

Thinking strategically

Use of DoE speeds up formulation development, but more is needed and more is possible if one thinks strategically about formulation development.

Over the years, it has been recognized that experimentation is more effective when it is approached with a strategy in mind. To be effective, any strategy must recognize that the design, or sequence of designs, should match the experimental environment; that experimentation is sequential; and that the DoE tools must be embedded in the strategy and linked and sequenced to guide the experimenter.

This experience leads to the following principles, which can enhance experimental strategies:

- Plan ahead; define the series of experiments needed to satisfy the objective of the program.
- At the beginning, include (or at least consider) all factors (Xs) that may possibly be important. Recall the Pareto effect, and the fact that most of the variation will be caused by a small subset of the factors so that, as one moves through the experimentation, the important factors will be discovered and tested further in later experiments.
- Don't spend all resources on a single experiment: an issue is rarely resolved in a single experiment.

A strategy that uses these principles was developed at DuPont in the 1960s, and offered in public workshops beginning in the 1970s. In the case of formulation, this strategy identifies two experimental environments: screening and optimization. The objective of each of the phases and the designs used is summarized in **Table I**.

Briefly stated, the screening phase explores the effects of a large number of ingredients (components) with the objective of identifying a smaller number of components to study further in optimization experiments. Additional screening experiments involving additional factors may be needed when the results of the initial screening experiments are not promising. On several occasions, the screening experiment solves the problem.

Predictive model development

In the optimization phase, a predictive model is developed for the system that can be used to find useful operating conditions using response surface contour plots and perhaps mathematical optimization. The result is the design space.

The end result of each of these sequences is a completed project. There is no guarantee of success in a given instance, only knowledge that the DoE strategy will "raise your batting average" (8). The strategy used depends on the experimental environment, which includes the objectives of the experimental program, the nature of the components (Xs) and responses (Ys), resources available, quality of the information to be developed, and the theory available to guide the experiment design and analysis. A careful diagnosis of the experimental environment along these lines can have a major effect on the success of the experimental program.

Martinello *et al.* (9) presented a pharmaceutical tablet study that investigated the formulation involving the compound paracetamol, which was known to have poor flowability (a measure of how well the materials flow through the tableting equipment) and compressibility properties. The study involved seven ingredients, varied over the ranges that are shown in **Table II**.

Nine responses were measured. The focus of the following discussion will be for illustrative purposes, the repose angle response (**Table III**). A 19-blend extreme vertices design shown in **Table III** was used to design the formulations to be tested. This design was selected using the D-Optimality criterion.

As in any screening experiment, it is necessary to know

Table III: Pharmaceutical tablet compactability study design.

Blend	Microcel	Kollydon VA64	Flowlac	Kollydon CL30	PEG 400	Aerosil	MgSt	Repose Angle
1	0.58	0.165	0.125	0.05	0.05	0.015	0.015	20.93
2	0.615	0.25	0	0	0.1	0.03	0.005	18.87
3	0.5	0.25	0.245	0	0	0	0.005	43.87
4	0.5	0.25	0.025	0.1	0.1	0	0.025	45.80
5	0.595	0.25	0	0.1	0	0.03	0.025	12.23
6	0.5	0.1	0.245	0	0.1	0.03	0.025	10.73
7	0.875	0.1	0	0	0	0	0.025	42.9
8	0.58	0.165	0.125	0.05	0.05	0.015	0.015	16.97
9	0.5	0.1	0.245	0.1	0	0.03	0.025	16.90
10	0.525	0.1	0.25	0	0.1	0	0.025	39.67
11	0.865	0.1	0	0	0	0.03	0.005	14.07
12	0.595	0.25	0	0	0.1	0.03	0.025	14.60
13	0.58	0.165	0.125	0.05	0.05	0.015	0.015	16.43
14	0.5	0.25	0.245	0	0	0	0.005	45.43
15	0.695	0.1	0	0.1	0.1	0	0.005	43.77
16	0.58	0.165	0.125	0.05	0.05	0.015	0.015	18.0
17	0.695	0.1	0	0.1	0.1	0	0.005	48.1
18	0.515	0.1	0.25	0.1	0	0.03	0.005	16.93
19	**0.58**	**0.165**	**0.125**	**0.05**	**0.05**	**0.015**	**0.015**	**21.37**

what components are most important as measured by their effect (positive or negative) on the response. This information will enable one to answer the following questions:

- Can we select a formulation based on the results of this particular experiment?
- Is additional experimentation needed? If so, which components should be the focus of future experimentation?

It is not unusual for a screening experiment to provide the information needed to choose a desirable formulation. Such was the case in this particular study. If additional experimentation is needed, the screening experiment results provide a firm basis for designing the optimization experiment. In this case, a seven-term linear blending model of the following form was developed (**Equation 1**).

$$Y = b1X1 + b2X2 + b3X3 + b4x4 + b5x5 + b6X6 + b7X7 \quad \text{[Eq. 1]}$$

where Y represents the response of interest, in this case Y=Repose Angle; X1, X2 …. X7 represent the levels of the components, and the bs are regression coefficients associated with the Xs.

Martinello *et al.* (9) developed equations such as **Equation 1** for each of the responses and used the equations to develop an optimal formulation, which, when tested, produced measured responses that were very close to those predicted by the linear blending model. Thus, in this case, additional experimentation was not needed.

Calculating component effects

The principal output of a screening experiment is the component effects. The component effects shown in **Table IV** for the repose angle response were calculated using methods proposed by Cox (10). The linear blending model defined by **Equation 1** fit the data with an adjusted R-Square value of 82%, a respectable value for a screening experiment. The overall model gave a statistically significant fit to the data (p=0.000).

Figure 1: Pharmaceutical tablet compactability study design: plots of predicted repose angle-versus-component levels.

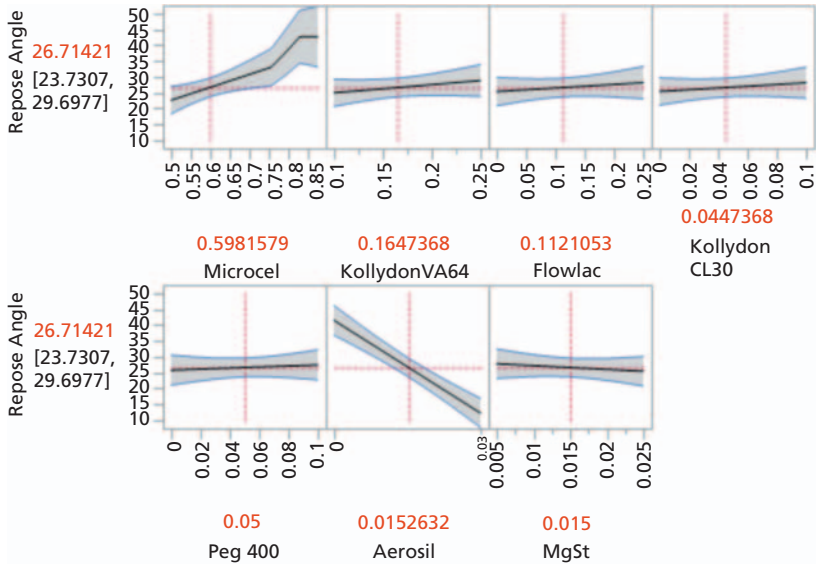

Table IV: Pharmaceutical tablet compactability study: component effects for repose angle.

Component	Effect	p-Value
Microcel	15.23	0.018
KollydonVA64	3.89	0.260
Flowlac	2.81	0.434
KollydonCL30	2.76	0.413
PEG400	1.66	0.635
Aerosil	-29.27	<.0001
MgSt	-2.38	0.484

In **Table IV**, note that the Microcel and Aerosil have a significant effect on the tablet repose angle. The Aerosil effect is negative and much larger than the Microcel effect, which is positive. These effects are seen in the component prediction profile plots in **Figure 1**. Note that in **Figure 1** the effect lines for all the components except Microcel and Aerosil have a very small slope, indicating no effect.

Interpreting component effects

When evaluating component effects to better understand formulation systems, the following are recommended:

- Evaluate the component effects using the Cox effect directions to assess the nature and magnitude of the component effects as shown in **Figure 1** and **Table IV**.
- Study the component effects to identify components that may have equal values indicating similar blending behavior.
- Assess whether similar blending of these components is supported by subject-matter science and business knowledge. Components with effects that are not statistically significant identify components that have no effect. The response to finding components that have no effect will depend on the objectives of the experiment. Options include setting the component with no effect at any desirable level within the range studied. If zero is at or near the lower end of the range, one can consider removing the component from the formulation. In all cases, the selected action should take into account subject-matter science and business knowledge (8).

A formulation optimization case study

Hirata *et al.* (11) present an optimization case study focused on the development of a three-component sustained release tablet of chlorpheniramine maleate. The objective of the study was to find a formulation with a release rate >30 units. The ranges of the three components shown in **Table V** suggests the use of an extreme vertices response surface design.

These component ranges produce an experimental region that has six vertices (**Figure 2**). The region is irregular, and there are two pairs of vertices that are close together (points 2 and 3 and 4 and 5, **Table IV**). **Figure 2** shows the six vertices, the six-edge centroids, and the overall centroid, as well as the response surface contours that will be discussed later.

In a formulations experiment design made up of the six vertices, the six-edge centroids (including the two short edges) and the overall centroid, which was tested three times for a total of 15 blends, were evaluated. The design and release rate data are shown in **Table VI**. In this table, five of the design blends (5, 6, 10, 11, 12) have release rates > 30. This provides the scientist's assurance that the objectives of the study will be met, even before any statistical modeling and analysis are done.

Plots of predicted release rate versus component levels for each component are shown in **Figure 3** (sometimes referred as the prediction profile). In this figure, CP has a negative effect while MCC and PVP have positive effects. The component linear effects as measured along the Cox axes show that the CP effect (-16.5 units) is dominant as compared to the MCC and PVP effects which are 7.9 and 9.5 units, respectively. In formulation optimization studies, the quadratic model is the model of choice, particularly at

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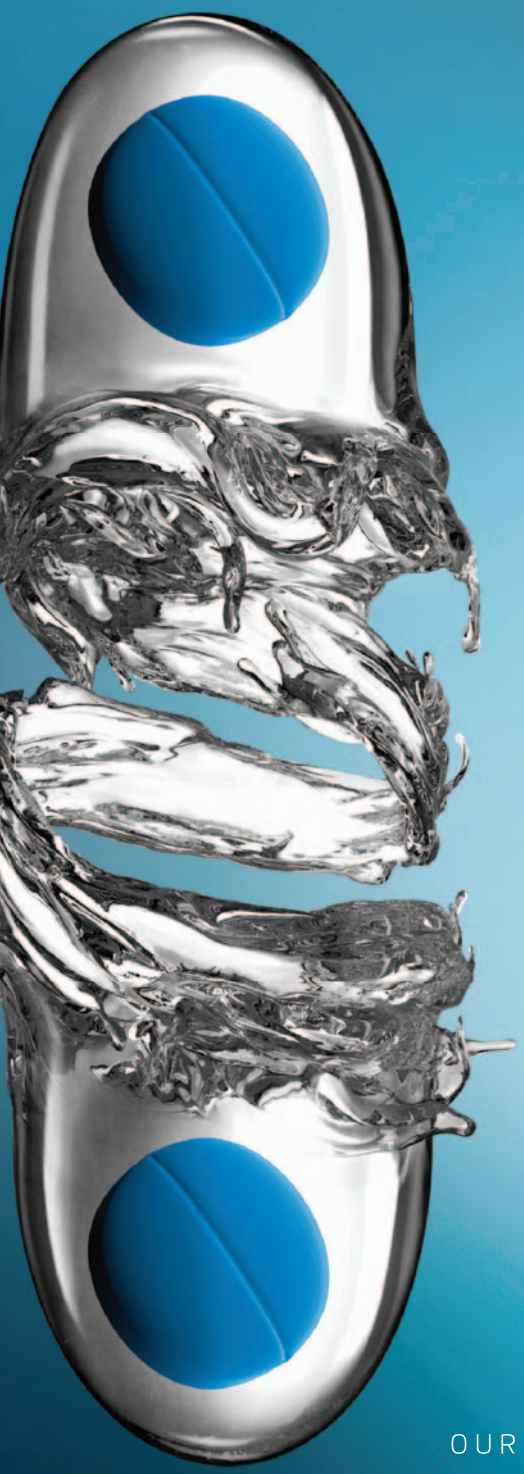

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Figure 2: Sustained-release tablet experimental region defined by component constraints and response surface contours.

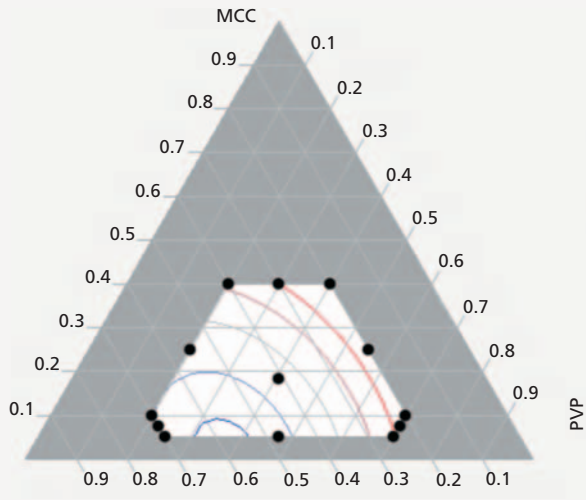

Figure 3: Predicted release-rate-versus-component levels plots along Cox axes. MCC = Avicel PH 105; MCC is Avicel PH 105; CP is Hiviswako 104; PVP is Providone K90.

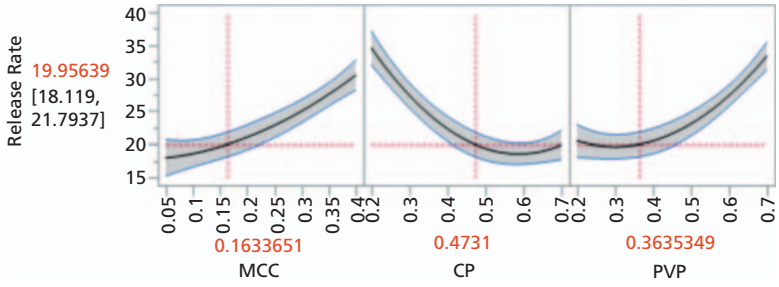

Table V: Components evaluation in optimization case study.

Component	Low level	High level
MCC (AvicelPH105)	0.05	0.40
CP (Hiviswako104)	0.20	0.70
PVP(PovidoneK90)	0.20	0.70

the beginning of the analysis process. The three-component quadratic blending model of the form is shown in **Equation 2.**

$$Y = b1X1 + b2X2 + b3X3 + b12X1X2 + b13X1X3 + b23X2X3 \quad [Eq. 2]$$

Where Y represents the response of interest. In this study case, Y=Release Rate; X1, X2, and X3 represent the levels of the components, and bs are model regression coefficients.

There is no guarantee of success in a given instance, only knowledge that the DoE strategy will 'raise your batting average.'

Evaluating fit

The fit of the quadratic model (Equation 2) gives a good fit to the data as judged by the adjusted R-square value of 94%. As expected, there was some significant curvilinear blending involving MCC and CP and PVP and CP.

The centroid blend was evaluated three times. These replicate blends enable us to test the lack-of-fit of the model. This test was not significant (p=0.638), providing further indication of the adequacy of the fit of the quadratic model.

The next step is to construct the response surface contours to identify the formulations that will produce release rates > 30 units. In **Figure 2**, over the design space, levels of CP < approximately 0.25 will produce release rates > 30. **Figure 2** shows contours for release rates of 18, 20, 24, 28, and 32; associated with decreasing CP moving left to right. The curved contour lines result from the curvilinear blending noted above. Components that blend linearly produce straight line contours. The fit of the model was checked by running two confirmation experiments (**Table II**, blends 16 and 17), which produced "observed" and "predicted" release rates of 32.7 vs 30.0 and 20.7 vs 20.0, respectively. These accurate predictions added further evidence of the adequacy of the model.

The right data in the right quantity at the right time

The strategy of formulation development described in this article enables formulation scientists to speed up formulation development by getting the right data in the right

Table VI: Sustained-release tablet development: extreme vertices design. MCC is Avicel PH 105; CP is Hiviswako 104; and PVP is Providone K90.

Blend	Point Type	MCC	CP	PVP	Release rate
1	Vertices	0.400	0.400	0.200	29.6
2	Vertices	0.100	0.700	0.200	19.9
3	Vertices	0.050	0.700	0.250	17.3
4	Vertices	0.050	0.250	0.700	29.3
5	Vertices	0.100	0.200	0.700	36.2
6	Vertices	0.400	0.200	0.400	38.2
7	Edge Centroid	0.250	0.550	0.200	20.9
8	Edge Centroid	0.075	0.700	0.225	21.4
9	Edge Centroid	0.050	0.475	0.475	20.2
10	Edge Centroid	0.075	0.225	0.700	34.3
11	Edge Centroid	0.250	0.200	0.550	33.9
12	Edge Centroid	0.400	0.300	0.300	31.0
13	Centroid	0.184	0.408	0.408	20.0
14	Centroid	0.184	0.408	0.408	22.7
15	Centroid	0.184	0.408	0.408	23.3
16	Confirmation	0.201	0.257	0.542	32.7
17	Confirmation	0.100	0.700	0.200	20.7

amount and the right time. In the process, the formulation scientist's "batting average" is raised (10).

Proven techniques, and available software

The strategy and methodology outlined here have been used successfully, and tested over time. They work, and there is software available to ease the computational burden, as well as to create graphics that aid in analyzing the data and visualizating the results. In short, the approach seems worthy of consideration by formulation scientists.

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Cleaning Validation for APIs

Michel Crevoisier and Thomas Peglow

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The industry needs a single standard cleaning limit at 25 mg/m².

Michel Crevoisier is former senior quality expert for Novartis Pharma AG, and **Thomas Peglow** is senior cleaning validation expert at Novartis Pharma AG, Switzerland. The views expressed in this article are those of the authors and not necessarily of their employers.

At home, when washing the dishes, do we ever consider what meal they will be used for next? When plates and cutlery are taken out of the cupboard to set the table, do we ever ask what they have been used for and whether they are clean enough for the gourmet course about to be served?

Are there different levels of cleanliness used for the dishes depending on the food served or the guests we entertain? Silly questions, apparently, but the industry's current approaches to pharmaceutical cleaning validation can often seem just as random. Cleaning limits for pharmaceutical manufacturing equipment are computed based on the previous and next products for every product change. As a result, it is often difficult to explain the cleaning and cleaning validation concept.

This article is about combining the simplicity of the household cleaning concept with the science needed to protect patients' safety. To reach this goal, it may be necessary to revisit a few traditional ideas about cleaning validation and to establish new principles. The focus will be on API manufacturing of small molecular weight substances (i.e., with industrial organic chemistry and the corresponding traditional plant equipment such as reactors, separators, crystallizers, centrifuges, filters, dryers, mills, and blenders, plus all the connecting pumps, pipes, and hoses). The size of the vessels typically ranges from 250 to 10000 L, and a manufacturing line can have up to several hundred square meters of product contact surface.

The change from product A to product B is not a frequent case

APIs are usually produced in multipurpose equipment. Several individual modules are concatenated to build a product-specific production line or train. After a campaign, the line usually gets disconnected and the individual modules, not always all of them, are reconfigured into a new line for the next product. Some products may use exactly the same production line as others, but most of the time, every product uses a somewhat different configuration of modules. Some equipment is used for many products; other parts are practically dedicated to a few or to only one product.

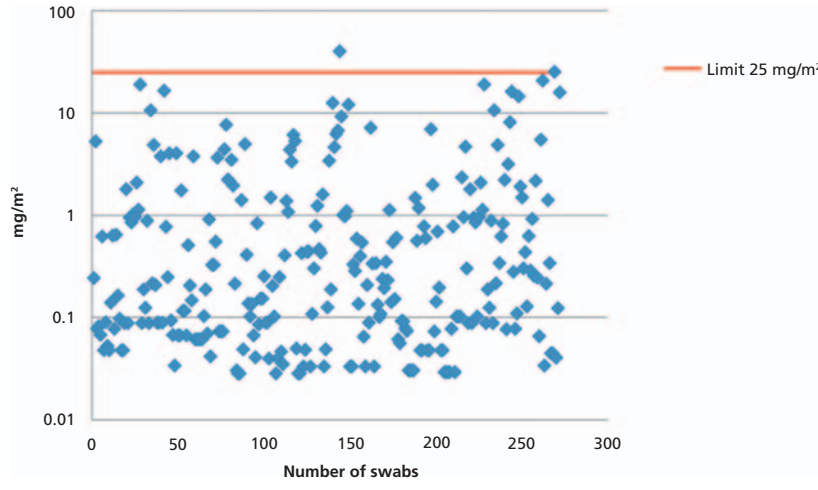
When a line is set up for product B, some parts will indeed have been used for product A right before; other parts, however, may have been in contact with product X, and mobile parts may be taken from the storeroom and have been used for product Y or Z months before. There is rarely a pure product changeover from A to B; in reality, the changes are from products A, X, Y ... to product B.

Similarly, when cleaning a piece of equipment, it is not always known what the next product will be. The change could be from A to the next products B, C, or D. This is particularly the case with interchangeable mobile equipment such as flexible hoses, filters, or tanks that go back to the storeroom after cleaning. Under such circumstances, a number of questions will arise, including the following:

- What was the previous product manufactured at the facility, and what will be the next one?
- How can one make sure that all parts are clean, to the right level for making the next product(s)?
- Can the cleaning validation concept be built and the cleaning limits computed based on the ideal product. change from A to B?

The following principles aim to answer these questions.

Figure 1: Graph of more than 250 swab results collected over a period of 18 months in multipurpose API unit A. Swabs were taken after using different cleaning procedures, after campaigns of different lengths, making different products, and from different pieces of equipment made of different material. The lowest values were often limited by the limit of quantitation of the analytical methods.



The cleaning procedure is independent of the following product(s)

Equipment cleaning should be thought as a reset function. The equipment is reset to a clean ground state form where it can be used for any product. Every piece of equipment labeled clean must be ready for use, no questions asked.

Consider the analogy with the household: doing the dishes, one doesn't ask what will be cooked the next day, and when taking clean plates out of the cupboard, it doesn't matter what the last meal was. A clean plate is a clean plate.

Cleaning without asking what the next product will be implies that setting the cleaning limit must be a comprehensive exercise that includes all products of a manufacturing unit. Quite often, the "cleaning validation runs" and the corresponding plans and protocols only consider the actual product change A to B, which leads to cleaning à la carte, asking: How clean does it have to be today?

Using the same cleaning procedure for different cleanings, it can happen that different limits must be met from one cleaning to the next, because the limits get recalculated each time for the actual, ideal product change. With such moving targets, it is impossible to properly validate a cleaning process.

Equipment cleaning should be thought as a reset function. The equipment is reset to a clean ground state form where it can be used for any product.

A standard cleaning limit (SCL) should be set, in mg/m2

Establishing a standard cleaning limit (SCL) for all the equipment is the core element of the cleaning concept (1). The SCL is the level of cleanliness (expressed in mg/m^2) that a production unit must maintain with every cleaning process, every time. The SCL applies to every piece of equipment, fixed or mobile, large or small, independently of the product changes.

What does the cleaning practice tell us?

Most production units will have collected cleanliness data, typically results of swab tests, over quite a long period. An example of such a data set is given in **Figure 1**. The example is from a relatively old manufacturing unit (Unit A), which uses traditional equipment for industrial organic chemistry. The cleaning procedures consist mainly of flushing and boil outs with solvents and manual scrubbing with water and a detergent.

FIGURES COURTESY OF AUTHORS.

Figure 2: Histogram with cumulated frequency of swab results from Figure 1. 75% of swabs gave ≤1mg/m², 95%≤10 mg/m².

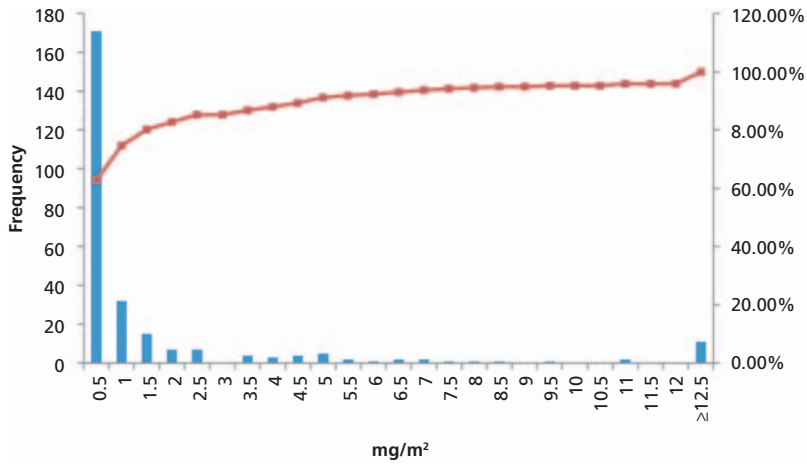


Figure 1 gives a good idea of the level of cleanliness this particular production unit can achieve. The values vary a great deal and the level of cleanliness that can reasonably be guaranteed is limited by:

- Physicochemical properties of the process residues
- Equipment design
- Cleaning methods.

The conclusion from **Figure 1** was that this particular production unit could be reliably cleaned down to 25 mg/m². Although much lower values than 25 mg/m² were often obtained (see **Figure 2**), 25 mg/m² is considered the unit's standard cleaning performance and so, for this unit, the SCL was set at 25 mg/m.²

Introducing an SCL opens the possibility of having a single cleaning limit for many different manufacturing units.

Based on reality, rather than theory

Setting the SCL in this simple and pragmatic way, solely based on experimental data, without any theoretical considerations, reflects acceptance of the variability and limitations inherent in current cleaning practice. However, this approach represents a radical change from tradition. Previously, the limit was calculated in the validation protocol that only considered the effective product change. The quality assurance (QA) department determined to what limit the equipment was to be cleaned at this one time, without considering the big picture of years of cleaning experience.

The theoretical safety requirements for a changeover from product A to B are known. Based on the permitted daily exposure (PDE) of A, the maximal safe carryover (MSC) of product A into product B can be determined by using **Equations 1.** Dividing the MSC by the product contact surface used to make B gives the maximum safe surface residue of A (MSSRA) on equipment used for B.

Applying **Equations 1 and 2** to all the theoretically possible product changes in a defined manufacturing unit yields the MSSR matrix. The MSSR matrix is the matrix of all possible required levels of cleanliness for a defined portfolio of products. See reference 2 for an example of a computed MSSR matrix.

$$MSC_A\,[g] = \frac{PDE_A\,[\mu g]\ \ Batch\ size_B\,[kg]}{Maximum daily dose_B\,[mg]} \qquad \text{[Eq. 1]}$$

$$MSSR_A\,[mg/m^2] = \frac{MSC_A\,[g] \times 1000}{Total\ surface\ for\ B\,[m^2]} \qquad \text{[Eq. 2]}$$

Figure 1 shows a graph of more than 250 swab results collected over a period of 18 months in multipurpose API unit A. Swabs were taken after using different cleaning procedures, after campaigns of different lengths, making different products, and from different pieces of equipment made of different material. The lowest values were often limited by the limit of quantitation of the analytical methods.

Risk assessment

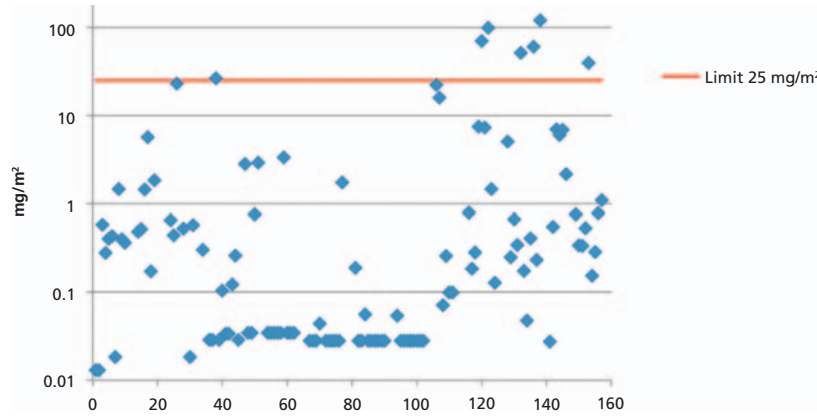
The risk of carryover contamination can be assessed by comparing the level of cleanliness that can be reasonably expected (the SCL) with the cleanliness required by the MSSR matrix (2). During risk assessment, the following should be addressed:

- Are the cleaning processes good enough to ensure safe changeovers? If not, is it reasonable to simply conclude that the cleaning procedures should be improved? Maybe there is room for improvement; but chances are that the cleaning processes have already reached their limits. If this is the case, can risk of the worst changeovers be mitigated by other means than cleaning?

- Can a few theoretical changeovers be eliminated from the MSSR matrix because they do not share any common equipment?
- Can manufacturing campaigns be planned in a way to avoid critical changeovers?
- Do certain products call for partially of fully dedicated equipment?

Such considerations should be summarized in a risk assessment document, which should be part of the cleaning validation master plan. Additional risk assessment can be done based on analysis of the swab results shown in **Figure 2**. The SCL of 25mg/m^2 is a safe limit, because the probability of a cleaning giving a swab result >25 mg/m^2 is <1%. Should a failure risk of 5% be deemed acceptable, the SCL could even be lowered to ≤10 mg/m^2. **Figure 3** shows swab data, as does **Figure 1,** but, in this case, they were measured in a different manufacturing unit (B) of the same company.

Figure 3: Graph of swab results collected in multipurpose API unit B under the same conditions shown in Figure 1. The values > 25 mg/m^2 were treated as deviations.



Setting the cleaning limit must be a comprehensive exercise that includes all products of a manufacturing unit.

The data for unit B are very similar to those for unit A and the SCL was also set at 25 mg/ m^2 for unit B. Because units A and B both manufacture small organic molecules, use similar equipment and very similar cleaning processes, it is not really a surprise that similar cleaning results are obtained.

Introducing an SCL opens the possibility of having a single cleaning limit for many different manufacturing units, which can help to further standardize cleaning validation. In fact, the SCL of 25 mg/m^2 was eventually introduced in five different manufacturing units.

With its general applicability and ease of use, the SCL concept can be compared to the classification system for cleanrooms, where the room class is independent of the room size or the nature and quantity of product that is handled in the room. The SCL is, similarly, independent of equipment size, products, or batch size.

Via the SCL, one can imagine a classification of API manufacturing equipment (e.g., in class 5, 25, and 50 mg/m^2). Such equipment classes, which in fact would reflect validated cleaning commitments, could be criteria to consider when allocating new products to manufacturing sites or outsourcing API manufacturing. Comparing the SCL and the MSSR matrix is a straightforward way to start a cleaning risk assessment and to implement the new EMA guideline on shared facilities (3). In addition, adopting the SCL offers a number of benefits. For example, it:

- Allows for a consistent level of cleanliness to be enforced over a whole production unit
- Simplifies cleaning validation because there is no need to compute and justify the cleaning limit in every single validation plan; the limit can instead be justified once in an appropriate document, (e.g., in the cleaning validation master plan)
- Allows manufacturers to standardize validation activities in the analytical laboratory: Specifications for swab tests are constant, as are the working ranges of high-performance liquid chromatography (HPLC) methods and when spiking coupons for recovery studies.

Last but not least, the SCL is a simple concept that is easy to understand and to explain.

Acknowledgements

The authors would like to thank Sébastien Schuehmacher, Michael Wölfle, and Markus Schaefer for their relentless cleaning efforts and their support in the development of the SCL concept, and to Ian Udri for compiling all the data.

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Four Challenges for Pulmonary Drug Delivery

Vince Russell

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Pulmonary drug delivery is becoming increasingly used. When developing pulmonary drugs, pharmaceutical chemists must consider drug absorption, control of particle size, suitable toxicology models, and patient compliance. The author reviews the issues specific to developing drugs designed for pulmonary delivery and considers how—with the right knowledge and expertise—these challenges can be overcome.

Vince Russell is director of Respiratory Discovery at Aptuit, www.aptuit.com/drug-design-and-discovery/therapeutic-areas/respiratory.

Respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and idiopathic pulmonary fibrosis are among the most serious and widespread healthcare challenges facing the developed world, accounting for more than 400,000 deaths in the European Union, equivalent to 8% of the total mortality figure (1). Such figures highlight the growing need for innovative and effective treatments. Pulmonary drug delivery is receiving increased attention as a non-invasive means for local treatment of a wide range of major lung diseases; this route of administration, however, poses additional challenges for medicinal and formulation chemists.

Defying conventional drug design wisdom

The lungs have the ability to deliver compounds into the circulatory system quickly; oxygen is transported into the bloodstream and carbon dioxide is offloaded in each breath.

But when treating respiratory diseases with extracellular targets, it's vital that topically acting drugs remain and act within the lungs. Absorption into the body could cause significant side effects, such as those affecting the digestive, cardiovascular, and central nervous systems, depending on the mechanism of the drug administered, as well as off-target effects. This challenge is at odds with the goal of conventional orally administered drug design, where medicinal chemists aim to modify the chemical properties of an API to improve absorption and bioavailability within the body.

When predicting the suitability of molecules as orally administered drugs, medicinal chemists often consider a set of four approximations to predict absorption in the gut, known as Lipinski's Rule of Five. Lipinski's rules state that an orally active drug should have no more than one violation of the following criteria:

- A molecular mass less than 500 Daltons
- An octanol-water partition coefficient (log P) not greater than five
- No more than five hydrogen bond donors
- No more than 10 hydrogen bond acceptors.

But for extracellular luminal targets, to develop APIs that are less easily transported out of the lungs, it's necessary to use molecules that defy these rules. Larger compounds, for instance, are less able to cross the epithelial barrier, meaning they will be less easily absorbed into the bloodstream. Likewise, less lipophilic APIs will find it harder to penetrate the airway lining, remaining at the site of action for longer.

To minimize systemic exposure, it's again important to go against conventional orally active drug design thinking. Devel-

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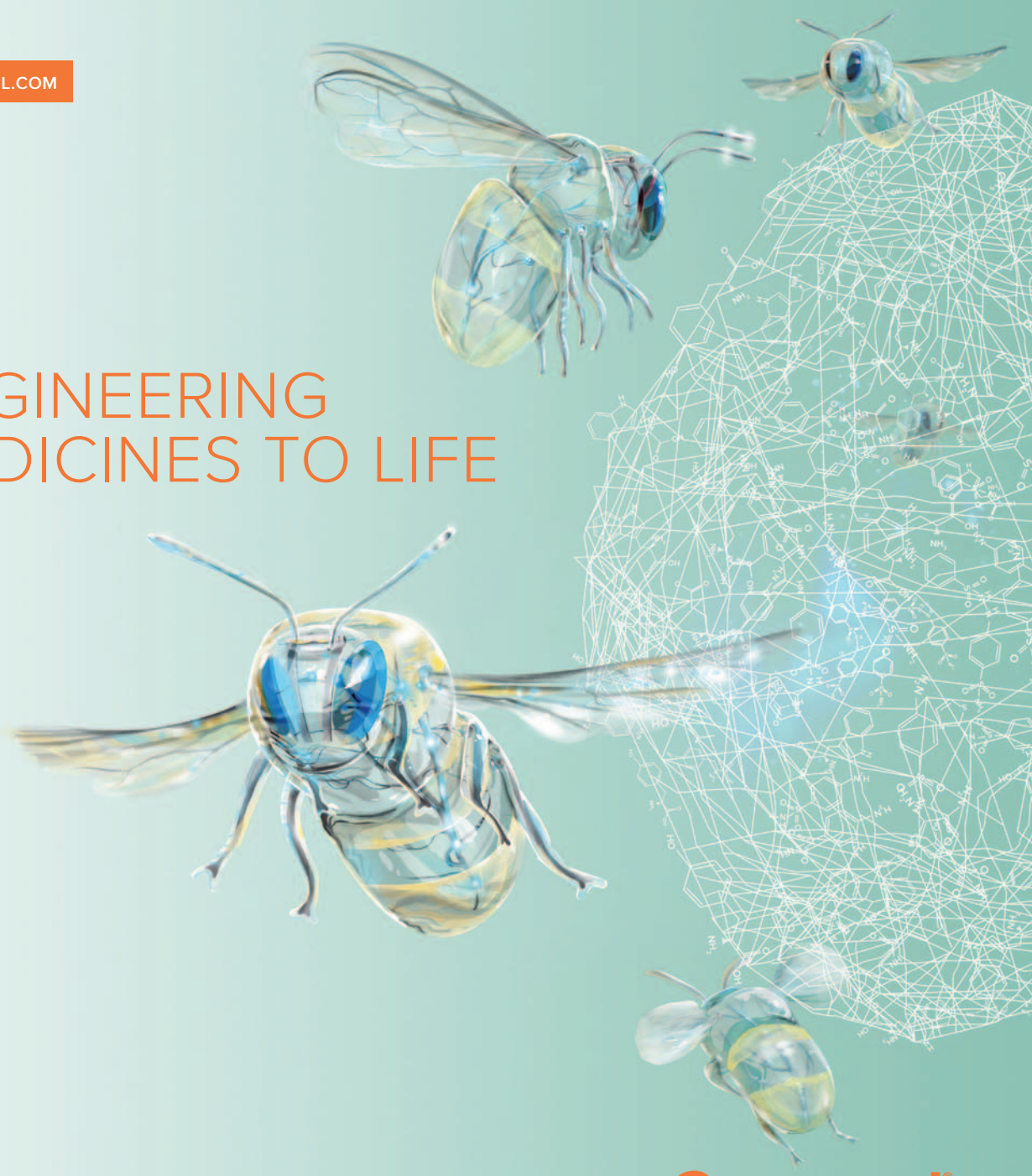

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oping drugs that won't be easily absorbed in the gut, which may be highly plasma protein-bound and/or rapidly metabolized and excreted, will be more successful at limiting the potential for treatment side effects.

Getting physical form right

The delivery of therapeutic agents as aerosols using metered dose (MDIs) or dry powder inhalers (DPIs) can be very effective for administering drugs locally to, or systemically through, the lungs. A key challenge, however, is to generate drug particles of a suitable size range.

Aerosol particle size affects both the dose deposited and the distribution of aerosol particles in the lungs and must be carefully optimized. Large-sized particle aerosols predominantly deposit on central airways with more drug deposited per unit surface area, whereas finer aerosols tend to be distributed in more peripheral airways with less drug deposited per unit surface area (2). Both of these factors can affect therapeutic efficacy, with the effects of distribution of a particular treatment strongly dependent on the location of the target receptors within the lung.

Control of particle size is also an important safety consideration. In the humid environment of the respiratory system, drug particles may readily stick together, potentially causing irritancy issues in addition to a reduction in efficacy.

Various micronization technologies based on air jet-milling are available for the preparation of suitably sized nanoparticles used for pulmonary drug delivery. These processes, however, do not always result in optimal particle properties, and they often create disordered surfaces that can cause recrystallization of the material during shelf storage, which subsequently affects product performance. Post-micronization treatment, designed to stabilize the material surface and reduce this physical instability, is therefore an important step that must often be considered.

Developing suitable animal models

It's often not possible to predict which particular form of the drug is going to cause problems until preclinical toxicology studies are undertaken. Robust, readily available predictive assays capable of quickly determining which form of a molecule is going to cause problems are essential. Developing animal models where drugs are administered intra-nasally or intra-tracheally requires careful planning and technical expertise. As it is inherently necessary for animals to breathe in while the drug is administered, multiple factors must be considered, including dosage timing, volume, and depth of anesthesia.

It's worth noting that even before planning formal preclinical toxicology studies, it's important to have a good understanding of how a drug might act *in vivo*. Significant amounts of time and resources can be saved through the use of simple and qualitative comparisons of candidate drugs early in the drug development process. These simple studies can offer an early indication of signs of lung irritation or inflammation, and this knowledge can guide development decisions and minimize the potential for unexpected and costly failure at later stages.

Overcoming compliance issues

When developing local treatments for respiratory diseases, it can be beneficial to target multiple biological pathways. In the treatment of COPD, for instance, long-acting beta-2-agonists and muscarinic acetylcholine antagonist bronchodilators are more effective when used in combination to relax the muscles that tighten around the airways (3, 4). Many asthma treatments employ both bronchodilators and anti-inflammatories, such as corticosteroids, which offer improved benefits when taken in combination.

However, the requirement for multiple drugs to be administered can have a negative impact on patient adherence to treatment regimen. With ease of convenience an important factor influencing compliance (5), a patient who must take two inhalers containing separate medicines may therefore be less likely to follow treatment. This issue may contribute to the relatively high rates of nonadherence to asthma medication regimens, with nonadherence figures as high as 70% reported (6).

One way to overcome this challenge could be to develop a single drug molecule that targets multiple mechanisms. Bifunctional muscarinic antagonist-beta agonists (MABAs) are a novel approach to dual bronchodilator therapy, which may offer greater efficacy than single mechanism bronchodilators with equal or better compliance. Such approaches could also open up the possibility of triple combination therapy when used in combination with a second molecule, such as a corticosteroid.

When opting for pulmonary drug delivery for treatment of lung diseases, it is also important to consider the impact of the condition or effect of age on the patient's ability to inhale the compound. If the lung function is compromised, the ability to get enough compound to the right place is potentially an issue. Some older patients may lack respiratory muscle strength to use DPIs correctly. In these cases, inhalation using a nebulizer may need to be considered.

Conclusion

Pulmonary drug delivery is becoming an increasingly used non-invasive route of administration to treat widespread and debilitating lung diseases. However, when developing treatments that rely on this delivery mechanism, it is important to consider the key challenges associated with this approach. By partnering with experienced industry experts, these challenges can be overcome, helping to bring safe, effective treatments to patients more rapidly and affordably.

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QbD: Improving Pharmaceutical Development and Manufacturing Workflows to Deliver Better Patient Outcomes

Martin Koeberle and Wolfgang Schiemenz

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Implementing quality by design in product design and formulation and manufacturing workflows can help improve efficiency and shorten development times.

Martin Koeberle

Wolfgang Schiemenz

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Quality has always been a key focus for the pharmaceutical industry, with drug developers traditionally using late-stage quality testing to ensure medicines are safe, reliable, and effective for patients. However, there is a growing appreciation within the industry that this approach may not be the most effective or efficient to safeguard quality. After all, quality cannot be "tested into" a product—it should be there by design from the very beginning of product development right up to the manufacturing process.

The adoption of advanced process analytical technology (PAT) throughout the pharmaceutical value chain is now enabling forward-looking companies to move away from traditional quality testing methods and instead, use systematic, data-driven strategies to deliver quality outcomes. One such concept that is widely used in other industries and has been gaining traction within the pharmaceutical industry is quality by design (QbD).

In this article, the authors discuss the advantages of adopting a QbD approach, and how this concept can be applied throughout formulation and manufacturing workflows.

Moving away from traditional product development

QbD essentially involves designing quality into workflows upfront. The concept is aligned with the "Design for Six Sigma" paradigm, originally developed in the automotive industry. It represents a radical shift away from the empirical-based methods traditionally used in product development and manufacturing and has since been implemented across a variety of other manufacturing environments.

With a QbD approach, the product's essential attributes are first defined. Risk and data analysis are then used to understand how the processes affect the product characteristics. QbD provides a robust framework for the design and implementation of processes that achieve a consistent level of quality and meet predefined standards. PAT plays a crucial role in the implementation of QbD—it allows the development and manufacturing processes to be monitored and optimized through real-time controls.

Using this data-driven approach to improve manufacturing and development workflows can save time and money in the long run.

The main issue with late-stage quality analysis is that it only detects and removes substandard products—it doesn't prevent them from being created in the first place. As pharmaceuticals become increasingly complex, it's more important than ever that quality is designed into the products from the initial concept to ensure patient safety.

In recent years, key regulatory authorities, including FDA and the European Medicines Agency (EMA), have actively encouraged QbD and PAT through a number of initiatives. FDA recently began updating existing regulations to encourage the adoption of new analytical technologies that facilitate risk-based processes, and in the past few years, the agency has also released two QbD case studies for abbreviated new drug applications. Recognizing that QbD offers significant improvements in quality, regulatory authorities are now beginning to insist that pharmaceutical developers and manufacturers adopt QbD throughout the value chain, especially given that the technology needed to implement this approach is widely available.

QbD provides the flexibility to operate within a broader design space when changes to the manufacturing process occur that are outside one's control.

Stages of a QbD-based product development

There are extra steps involved in the initial QbD-based product development. Additional upfront investment in terms of time, money, and resources will be required, but it protects against variability later on; it also minimizes risk, reduces waste, and saves time in the long run.

Through detailed characterization of materials such as APIs and excipients, the critical quality attributes (CQA) are defined. CQAs are the chemical, physical, biological, and microbiological attributes that may significantly affect the quality of the finished product. This information enables the identification of critical process parameters (CPPs), which are the key variables that affect the production process. CPPs can be monitored to detect any deviation in manufacturing processes, and active control of these CPPs can counteract these deviations in order to ensure product quality and that CQAs are met.

For example, Hermes Pharma was involved in developing an effervescent cough and cold formulation containing three APIs—acetaminophen, caffeine, and phenylephrine. Given the low concentration of phenylephrine, in the final product, a key challenge was to ensure content uniformity for all three APIs so that the product delivers reliable and reproducible efficacy when taken by patients. A QbD approach was adopted to improve the blend homogeneity of the APIs within the final product.

Figure 1: Near infrared spectrometer attached to a production scale blending container. The spectrometer wirelessly transmits data for real-time analysis.

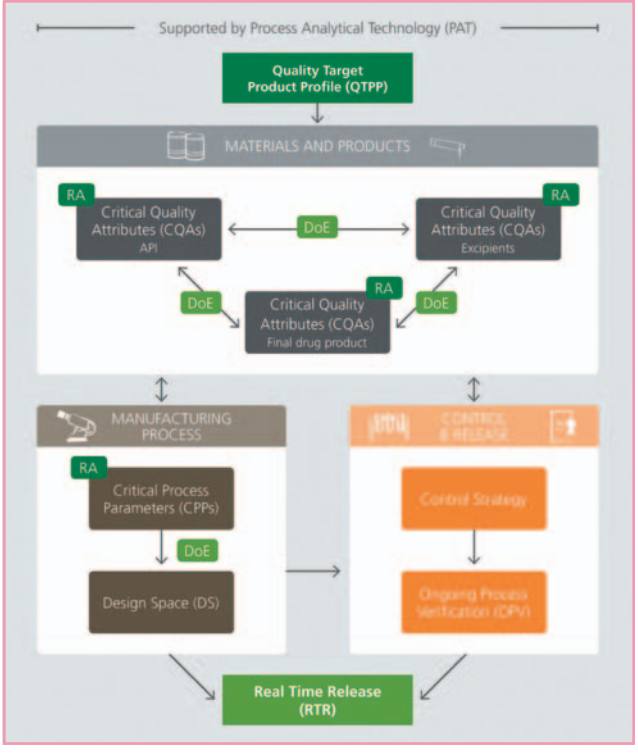
The formulation involved three separate blending steps. Prior to adopting QbD, the blending time and speed would have been based on the formulator's experience, rather than being verified by experimental investigation. With the QbD approach, monitoring of the mixture at various locations within the container was carried out using high performance liquid chromatography (HPLC) for the initial blending steps and near infrared (NIR) spectrometry for the final blending process (see **Figure 1**). This data-driven approach meant that only when acceptable levels of blend homogeneity had been reached would the blending process continue to the subsequent step, resulting in more consistent levels of product quality.

Easier scale-up

In most cases, transitioning from laboratory scale to mass production is rarely straightforward. However, scaling up is often significantly easier when QbD is employed, because the manufacturing process is better understood. It reduces the risk of encountering unexpected problems that negatively impact on production throughput and timescales.

FIGURES ARE COURTESY OF HERMES PHARMA.

Figure 2: The potential approaches for quality-by-design (QbD) implementation within a pharmaceutical development and manufacturing environment. RA is risk assessment; DoE is design of experiments; API is active pharmaceutical ingredient.



In the effervescent cough and cold remedy example mentioned earlier, the adoption of QbD significantly reduced the time required to optimize the scale-up process. By monitoring the CPPs throughout the multi-step process, the formulators were able to gain an understanding of the main contributions towards blend inhomogeneity. And by pinpointing issues specific to a particular step in the process, attention could be given to the factors involved, which helped overcome the challenges during scale-up. Without QbD, scaling up would have been based on a trial-and-error approach and would have likely taken considerably longer to optimize.

Simplifying regulatory compliance

Another benefit of having a good understanding of the CQAs and CPPs is the ability to easily establish a formulation and process design space that ensures compliance with the quality target product profile. Essentially, the need to register later adjustments with regulatory bodies after large-scale production has begun can be avoided, which is important as such revisions can lead to significant delays when it comes to bringing a product to market. Moreover, by using QbD, risk can be managed more effectively and it will be easier to determine exactly which product changes will require additional regulatory submissions.

QbD also provides the flexibility to operate within a broader design space when changes to the manufacturing process occur that are outside one's control. For example, at Hermes Pharma, hot melt coating is used to mask the unpleasant metallic taste of acetylcysteine in the production of a mucolytic product. However, it was discovered that the particle size distribution of the API varied between batches of the raw material—a situation that often occurs, because in many cases, suppliers do not fully specify the particle size distribution of their APIs. As a result, if the same amount of coating was applied to each particle, the coating thickness would vary and the unpleasant taste could come through. However, because QbD was applied together with PAT, the formulators were able to screen the particle size distribution of the incoming API and categorize these into distinct classes with an associated coating method. This approach provided a more consistent coating layer irrespective of particle size.

QbD approaches based on process analytical technologies facilitate real-time release testing.

If only one process was designed for a very narrow particle size range, the unsuitable particle size fractions would have to be discarded by sieving, which is of course not cost efficient. Alternatively, the formulator would have had to agree upon a very specific particle size with the supplier, which would incur additional costs. Working within a predefined and regulatory-approved design space avoids the need to apply for additional regulatory approval when changes in raw material specifications are encountered.

Other benefits of QbD

QbD approaches based on PAT also facilitate real-time release testing. This approach gives manufacturers more timely information on product quality and means that any manufacturing problems can be dealt with faster, in a more informed manner.

QbD also puts in place the quality assurance framework necessary for continuous process improvement. Compared to traditional batch testing, continuous process verification is much more able to push the processes towards optimization and maintain manufacturing parameters within acceptable limits. It also reduces the sampling effort, further boosting process efficiency.

All of these process improvements mean that patients will benefit from an enhanced level of quality in their medicines, ensuring that the medicines are consistently safe and effective. As a result, customers benefit from a more reliable supply capability, preventing out of stock situa-

tions where product batches need to be destroyed due to poor quality.

A stepwise approach to implementing QbD

There are three key stages in implementing a QbD approach to pharmaceutical development and production (see **Figure 2**):

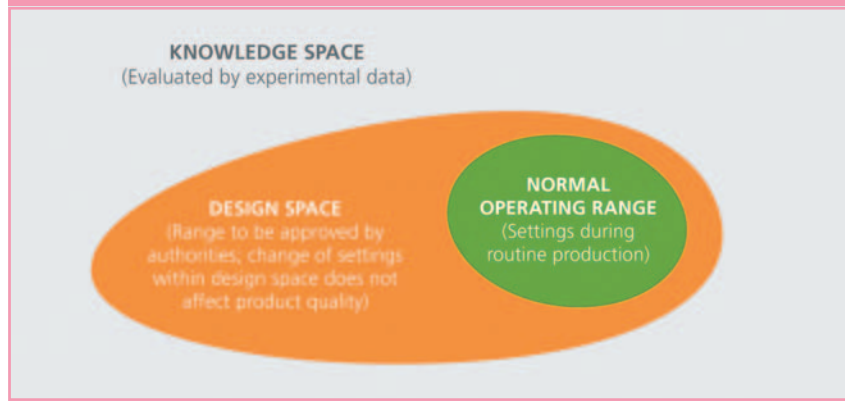
- Initial product profiling, risk analysis, and CQA/CPP determination during early development
- The design of experiments and the definition of possible and meaningful design spaces during the formulation/manufacturing development phase
- The establishment of a manufacturing and control strategy during scale-up and routine production. Manufacturing is also supported by ongoing process verification to ensure continued operation within the defined parameters.

At Hermes Pharma, the first step in our development programs is to establish the quality target product profile (QTPP) for the product. The pharmacological and patient requirements as well as quality are considered in advance of manufacture, hence, providing a starting point for identifying CQAs in the next step. This is followed by risk-based characterization of APIs and excipients, including an assessment of factors such as particle size distribution, morphology, processability, and batch-to-batch or supplier-to-supplier variation.

Risk analyses are also performed to determine CQAs for the pharmaceutical product. The goal is to study and control any factor—be it physical, chemical, or microbiological—that could affect the quality of the product. It's important to study APIs and excipients both in isolation and in combination to define their characteristics in as much detail as possible. Failure to keep these factors within the set boundaries creates the risk of manufacturing substandard products that can lead to manufacturing downtime or increased costs, and potentially harm supplier relationships. CPPs are variables contributed by the manufacturing process with the potential to impact the CQAs, resulting in a low-quality product. The greater the potential CQA impact, the more closely the CPP has to be controlled.

Next, the design space is defined. For example, the design space could be the relationship between specific process inputs and the CQAs. If the design space is developed accurately and all essential aspects of the process are within the design space, then the CQAs must be acceptable. The design space enables manufacturers to demonstrate to regulatory bodies a comprehensive understanding of their process. The regulatory body then approves the design space as an operational range, giving manufacturers the flexibility to operate provided the workflow remains within that range (see **Figure 3**) and avoid having to submit revised information to the regulatory authorities.

Figure 3: The relationships between normal operating range, the design space, and the knowledge space that evolves during the product development process.



Then, using the knowledge gained from the previous steps, together with the CQAs and CPPs, a control strategy is established. This control strategy must be defined in order to determine which analytical methods are required and where in the process they will be employed. PAT enables the control strategy to be further improved, as it facilitates the monitoring and control of the production processes in real-time.

To maintain product quality across all batches, ongoing process verification should be performed. Unlike traditional verification approaches, such as the "three golden batches" method, which focuses on analyzing the first three batches only, continuous process verification does not treat validation as a discrete exercise. This way, the manufacturing processes are operating at the very highest levels of quality for the industry.

Conclusion

QbD looks set to become increasingly important for the pharmaceutical industry as more and more companies are looking to boost production output, reduce throughput times, and lower costs by shifting from batch production to continuous manufacturing. However, for these "always on" processes, it just isn't possible to perform quality testing within a series of continuous process steps in the same way as it is following each operation of a batch process.

Additionally, as FDA, EMA, and other regulatory bodies further scrutinize production processes to ensure the highest levels of safety, QbD will make it easier for companies to demonstrate that they are operating within acceptable limits. As regulatory authorities start to insist that companies design quality into products at every stage of the pharmaceutical value chain, the use of QbD will become ever more important. **PT**

A Multifunctional Mineral Excipient

Carolina Diaz Quijano

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The development of orally disintegrating tablets (ODTs) is a demanding process and requires two seemingly contradictory product attributes: fast disintegration and high mechanical strength. High compression forces result in harder tablets but increase the disintegration time. Consequently, ODTs with optimal disintegration characteristics are often friable and lack mechanical stability in regular packaging. Omya has developed functionalized calcium carbonate (FCC), a multifunctional excipient that can overcome these challenges. FCC provides high porosity, which enables fast disintegration, and excellent compactibility that results in harder tablets at low compression forces. FCC particles can also be loaded with certain APIs and can thus be used as a drug carrier.

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Orally disintegrating tablets (ODTs) are becoming increasingly important in the global pharmaceutical market for both prescription and over-the-counter medications because they can significantly improve patient compliance. They can be swallowed without the need for water, are generally smaller, and have good mouthfeel. Such properties make ODTs particularly convenient for children and the elderly, especially when a flavor is also incorporated into the formulation. In addition, they are the delivery format of choice for people who want to take their medicine "on the go" and are particularly helpful for patients who have difficulty swallowing—a complication associated with a number of age-related conditions, including stroke and Parkinson's disease.

ODTs can be manufactured using various different techniques, such as tablet molding, freeze drying, spray drying, or direct compression. The final form—tablet or granule—has to deliver the active ingredients rapidly, but depending on the technique used, it may be associated with low mechanical strength, high production costs, or inferior stability. From the perspectives of cost and simplicity, the preferred method of preparing ODTs is direct compression. However, the disintegration capacity of ODTs produced in this way is limited by the size and hardness of the resulting tablets (1, 2). The challenge, therefore, when compressing ODTs is ensuring a structure that enables fast disintegration without affecting the hardness of the tablets. Developing a dosage form with these properties requires an excipient that offers optimum cohesiveness for compaction.

Properties

It can be difficult to find multifunctional excipients that do not add to the burden of an already extensive regulatory filing. Functionalized calcium carbonate (FCC) offers the advantage of being a structured mineral comprising calcium carbonate and hydroxyapatite, both of which are monographed minerals. FCC is manufactured from high-purity calcium carbonate that undergoes surface recrystallization (**Figures 1 and 2**). This process can be controlled

to obtain specific surface areas ranging between 30 and 180 m^2/g, a median particle size distribution of between 2 and 30 µm, and porosities of higher than 60%. FCC particles are characterized by an external lamellae structure and an internal network of interconnected pores.

In contrast to other porous excipients, FCC has a lamellae morphology, which provides plenty of surface contact points among the particles, ensuring interlocking during dry granulation in roller compactors. This structure facilitates the production of granules by dry granulation. After milling and sieving, the granules are ready to be mixed with APIs and can be compressed into ODTs. Thus, ODTs manufactured with FCC feature both high porosity and high levels of hardness.

Loading capability

Researchers at the University of Basel in Switzerland investigated the feasibility of using a particular grade of FCC as a carrier for poorly water-soluble APIs. Ibuprofen (IBU), nifedipine (NP), losartan potassium (LP), and metronidazole benzoate (MBZ) were selected as model substances to investigate drug loading (3). The team analyzed the loading capacity of FCC, the dissolution performance of the formulation, and whether the drug was loaded in its amorphous or crystalline form. The four APIs were dissolved in methanol or acetone and mixed with FCC. Using a rotary evaporator to control the pressure, the FCC-API particles were loaded with 25 to 50% (w/w) of each API, and afterwards the solvents were removed. For reference, the scientists also created FCC-API mixtures that contained equivalent API fractions but were not subject to a specific loading strategy. Loading efficiency was assessed using a scanning electron microscope (SEM). The presence of particle agglomerates or drug crystals outside the FCC particles indicated the maximum loading capacity. It was shown that the particles can be successfully loaded with up to 40% (w/w) API. The team also observed a reduction in intraparticle porosity after drug loading (63% for MBZ, 58% for IBU, 50% for NP, and 35% for LP), which provided evidence of pore filling. Drug concentration was quantified by high-performance liquid chromatography (HPLC). In addition, the dissolution rate of FCC loaded with NP and MBZ was found to be faster than that of the FCC-API mixtures. Because only low percentages of amorphous NP (8.9%) and MB (12.5%) were detected, the authors concluded that the faster dissolution was related to the locally increased solubility caused by the larger surface area and not due to the presence of an amorphous API.

Compressibility

In another study (4), researchers examined the compressibility of tablets made using FCC granules and compared them with tablets made with either FCC in powder form, conventional calcium carbonate, mannitol, or microcrystalline cellulose (MCC). The tensile strength and the porosity of the tablets were analyzed across a broad range of compression forces. At low compression force, the tensile strength of tablets formulated with FCC powder or FCC granules was higher than that of tablets formulated with mannitol or calcium carbonate and was comparable to that of tablets formulated with MCC (see **Figure 3**). The FCC tablets also had a higher porosity than those containing the other excipients tested.

With FCC in the formulation, tablets were able to reach comparable or higher hardness than other formulations at lower compression forces, which allowed their porosity to remain higher than 50%. This porosity provides a large volume of voids for accommodating APIs.

In a second step, the researchers analyzed tablets formulated with paracetamol and one of the following: FCC powder or MCC. They concluded that despite the presence of an API, the decrease in porosity of the FCC tablets was significantly less than that of tablets formulated with MCC when compression force was increased. Additionally, the

Figure 1: Micrograph of natural calcium carbonate.

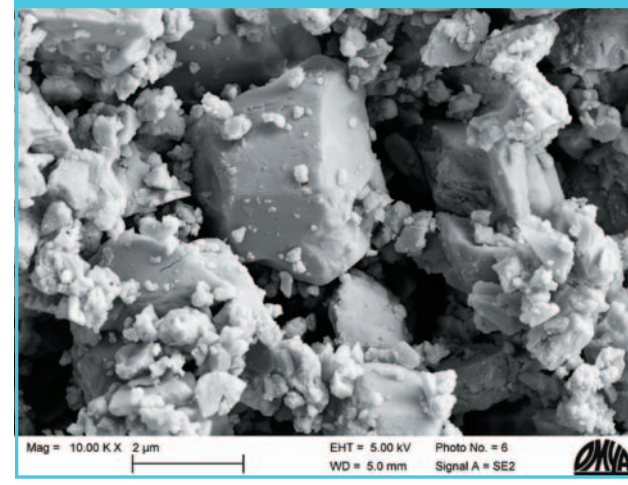

Figure 2: Micrograph of functionalized calcium carbonate.

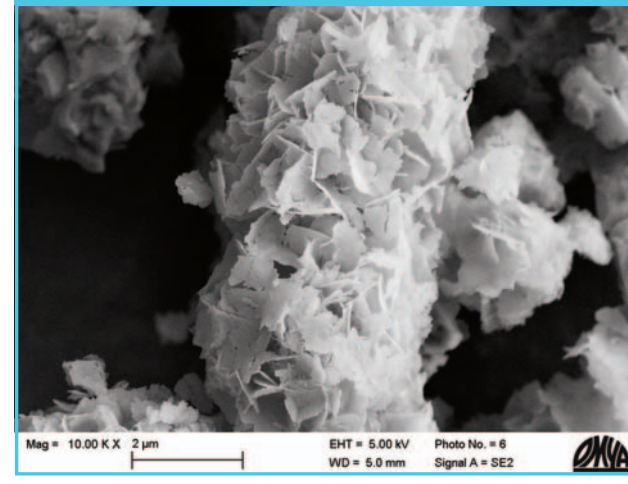

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Figure 3: Tensile strength vs. mean compression force for tablets made using functionalized calcium carbonate (FCC) and reference excipients. At lower compression forces, FCC tablets reach tensile strengths that are higher than or comparable to that of tablets formulated with other reference excipients. MCC is microcrystalline cellulose.

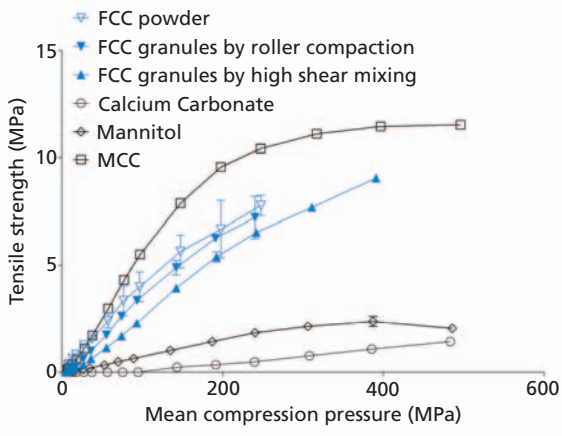
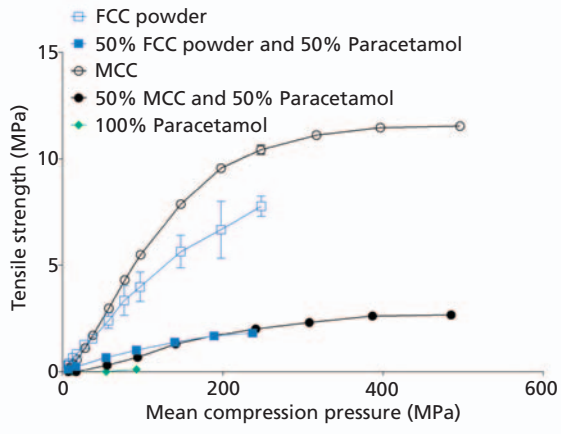


Figure 4: Tensile strength vs. mean compression force for tablets formulated with paracetamol and one of the following: functionalized calcium carbonate (FCC) powder or microcrystalline cellulose (MCC). The tensile strength of FCC tablets was comparable to that of tablets formulated with MCC.



tensile strength of the FCC tablets was comparable to that of tablets formulated with MCC (see **Figure 4**). Finally, the FCC tablets' combination of high tensile strength and high porosity indicated that FCC is suitable for use in ODTs as a pharmaceutical excipient.

Disintegration

In order to determine residence time, the scientists used a tensiometer to measure mass versus time, which in turn allowed them to study water uptake and disintegration behavior (5). They analyzed the disintegration kinetics of 24 different formulations and identified four patterns. Type I was considered the ideal behavior because it resembled the market formulation. Type II was characterized by very fast water uptake but no disintegration. Type III disintegrated in discrete steps, resulting in tablet pieces, while type IV disintegrated only partially. FCC exhibited a type I disintegration pattern, and its residence time was half that of the market formulation used as a reference.

FCC's direct compressibility into granules without the use of a binder and its high porosity, which allows faster water uptake, lead to a disintegration time that is twice as fast as the market reference product. In fact, orally disintegrating granules manufactured with FCC disintegrate in 2 seconds and their corresponding ODTs in less than 10 seconds (5).

Conclusion

ODTs manufactured with FCC can be produced by direct compression of a blend of FCC granules and the active of choice. The high porosity of ODTs formulated with FCC results in rapid disintegration and their high mechanical strength enables the use of regular bottles and blisters as packaging, which significantly reduces the overall cost of production compared to other ODT technologies.

Also, from a regulatory point of view, FCC has the advantages of being a co-processed excipient composed of only two monographed minerals. Moreover, it offers the possibility of multiple functionalities with simple chemistry and a straightforward granule and tablet manufacturing process. Additionally, it is possible to tailor the characteristics of FCC, such as specific surface area, particle size distribution, and pore size distribution, according to the requirements of various applications. Furthermore, unlike many similar materials, FCC has the advantage of being highly biocompatible. Its composition is basically that of mineral bone material: hydroxyapatite and calcium carbonate.

Bearing all of these advantages in mind, FCC is a promising excipient for dry oral dosage forms. It will be interesting to see what kind of formulations this mineral will make possible in the near future.

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2017 PLANNING GUIDE

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Welcome to CPhI Worldwide 2017

The Pharma industry is dynamic and prospering globally as demonstrated at CPhI events.

Orhan Caglayan
UBM EMEA

Welcome to this year's CPhI Worldwide! The event returns in a year when many developments and potential changes are sweeping across the global Pharma landscape, with Britain's exit from the European Union and the new administration in Washington being amongst the most notable. It has been a big year for Pharma, and an even bigger year for CPhI. Since the last CPhI Worldwide, we have seen both India Pharma Week and China Pharma Week integrated into their respective annual events—a true testament to the strength and global reach of the CPhI brand.

More generally, there has been a renewed confidence in the North American Pharma market combined with the three hotbeds of biotechnology—San Diego, San Francisco, and Boston—experiencing a notable resurgence. In fact, earlier this year we saw the launch of the inaugural CPhI North America, which was incredibly successful. North America, as the world's foremost Pharma economy, represented a natural progression for the CPhI brand.

A year of advances

But this year has seen many exciting developments throughout the globe, with the new Marketing Authorization Holder (MAH) pilot in China providing huge innovation opportunities for Chinese biotechs and generic drugs expanding from Japan, the United States, and Europe to the emerging markets. In addition to this, all of our global events have seen a surge in the number of bio and finished formulations attendees.

This year, we return to one of the most important global growth markets in the Pharma industry and Europe's largest pharmaceutical market, Germany. The country is perfectly placed in the center of Europe, making it an ideal location for the development, production, and sale of world-class pharmaceuticals, with the market predicted to be worth US$86 billion by 2021.

Industry predictions and promise

CPhI Worldwide is the world's largest pharmaceutical event and is seen as a bellwether of global Pharma's overall strength. For example, we recently took a look back over the past four years of the revered CPhI Annual Report and found that, remarkably, the majority of our experts' predictions have come to fruition. These included a predicted rise in US Food and Drug Adminstration warning letters, a boom in Pharma R&D, and the implementation of continuous processing for both APIs and finished products, amongst others.

I am truly excited to be representing this globally eponymous event, which incredibly has seen attendee numbers rise by 50% in just five years, to 42,000 in 2016.

I very much look forward to meeting all of you at this unmissable event. It's a truly dynamic time for the global Pharma industry, and CPhI Worldwide provides an opportunity to come together and focus on the latest trends, technologies, and insights. Above all else, it is a platform for the industry to drive forward new partnerships, do business, and grow.

Orhan Caglayan
Brand Director Europe, Middle East, and Africa
UBM EMEA

CPhI Worldwide 2017

Oct. 24–26, 2017
Messe Frankfurt, Germany

Co-located Events

- ICSE
- InnoPack
- P-MEC
- Finished Dosage Formulation

Education and Innovation

- Pre-Connect Congress (Oct. 23, 2017)
- Pharma Insight Briefings
- Women in Leadership Forum
- Innovation Gallery
- Innovation Tours

Business Meetings

Live Pharma Connect

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CEO, Diffway

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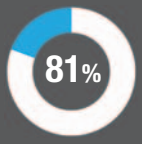
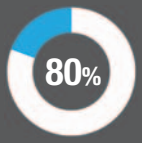
Cosmas Mukaratirwa
Managing Director, Cospharm

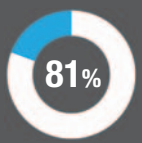
WHAT VISITORS SAID ABOUT THE 2016 SHOW*



rate CPhI Worldwide as the **leading global gathering** of the pharmaceutical industry



agree that CPhI Worldwide **is the most important show** in the pharmaceutical industry's calendar



believe that CPhI Worldwide is a **great show** to find new business opportunities

* *post show survey 2016*

WHY ATTEND CPhI?

- **Cost Effective: 42,000** pharma professionals from **150+** countries in one location
- **Entire pharma supply chain: 2,500+** exhibitors covering **ingredients, APIs, excipients, finished dosage, contract services, packaging, machinery** and more
- **Industry developments:** stay up-to-date on market news and trends during the **Pre-Connect Congress, CPhI Pharma Innovation Awards and Pharma Insight Briefings**
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CPhI Worldwide Highlights

In addition to a comprehensive exhibition, visitors to CPhI Worldwide can attend conference sessions, more than 80 expert-led informational sessions, and network with current and potential business partners.

Learn About Industry Trends at the Pre-Connect Congress

Monday, Oct. 23, 2017
Portalhaus, Frankfurt Messe

The 9th Annual Pre-Connect Congress offers keynote addresses, panel discussions, and thought-leader presentations on issues critical to the global pharma industry including pharmaceutical ingredients, outsourcing and manufacturing, drug pricing and policy, generic drugs, biologic drug development and manufacturing, finished drug products, packaging, and regulatory trends. See CPhI pages 6–7 for details.

Gain Insight on Crucial Pharma Issues

Tuesday, Oct. 24–Thursday, Oct. 26, 2017

In the Pharma Insight Briefings, experts will address a range of pharma topics in more than 80 free-to-attend seminars covering the latest trends, opportunities, and developments in Pharma. Topics include technologies for biologics drug development and manufacturing, packaging advances, serialisation, drug formulation, API development, excipients, sterilisation issues, and patient-centric design strategies. See CPhI pages 12–15 for details.

Exploring the Exhibition

Tuesday, Oct. 24, 2017: 9:30–17:30
Wednesday, Oct. 25, 2017: 9:30–17:30
Thursday, Oct. 26, 2017: 9:30–16:00
Halls 4, 6, 8, 9, and 10, Frankfurt Messe

CPhI Worldwide is home to more than 2500 exhibitors in 20 dedicated zones covering ingredients, APIs, excipients, finished dosage, contract services, packaging, machinery, and more. Visitors can meet with suppliers of fine chemicals and intermediates, biologic drug development products, drug delivery and devices, supply chain solutions, laboratory equipment and instruments, and contract services. See pages CPhI 9–11 for more information.

Networking in the Pharma Forum

Tuesday, Oct. 24–Thursday, Oct. 26, 2017

The Pharma Forum is dedicated to content, networking, sourcing innovation, and knowledge sharing. Located between Halls 8 and 9, the Pharma Forum features the following education and networking opportunities:

- Innovation Gallery, which displays new technologies
- Insight Lounge, a central area to relax, enjoy a free beverage, and provide feedback on the CPhI event and industry trends.

For more information visit: gotocphi.com/agenda

Recognising Innovation: CPhI Pharma Awards Gala

Tuesday, Oct. 24, 2017, 18:00–22:30
Intercontinental Hotel Frankfurt

The CPhI Pharma Awards honour innovation and excellence in 20 categories. Winners will be announced at the CPhI Pharma Awards Gala on Oct. 24. For additional information, see pages CPhI 16–17 or visit awards.cphi.com.

Scheduling Meetings at CPhI

CPhI offers multiple free tools to help you plan your time at CPhI Worldwide:

- Live Pharma Connect is a free online business matching tool for visitors and exhibitors to arrange on-site at CPhI Worldwide.
- The CPhI mobile app brings an interactive floorplan, exhibitor list, and the event agenda to your smartphone. Download the app from: www.cphi-app.com
- The Supplier Finder, an interactive floorplan allows visitors to search by company name, product name, or stand number to locate new or business partners.

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Women in Leadership Forum

Wednesday Oct. 25, 2017, 8:00–11:15
Portalhaus, Frankfurt Messe
Event sponsor: Dow Corning
In its fourth year, the 2017 Women in Leadership Forum will focus on strategies for building and improving diversity in Pharma, and takeaway solutions for initiating change in an organisation. This forum will look at best practices for diversity and inclusion. This event offers the opportunity to meet peers, hear from senior executives on promoting diversity in the workplace, share wins and losses, and assess strategies for career development. The registration fee for this event is €45.

Agenda

8:00–8:45
Breakfast and Networking

8:45-8:50
Welcome from the Chair
Dr. Amina Faham, global leader, R&D Pharma Applications, Dow Corning

8:50–10:00
Panel Discussion and Audience Q&A:
Increasing Women in the Pharma Leadership Ranks: Perspectives from Business Leaders
Moderator: Helena Demuynck, founding partner, Oxygen for Leadership
Panellists: Amina Faham, global leader, R&D Pharma Applications, Dow Corning
Jennifer O'Lear, director and chief diversity officer, Merck

10:00–10:45
Creating the Right Environment for Women to Succeed
Rosalie Harrison, Consultant, Borderless

10:45–11:15
Coffee and Networking

CPhI Worldwide 2017 Events (As of Aug. 23 2017)—View www.cphi.com/europe for schedule updates

Monday, Oct. 23, 2017		
Time	**Activity**	**Location**
9:30–19:00	Pre-Connect Congress	Portalhaus, Frankfurt Messe
Tuesday, Oct. 24, 2017		
Time	**Activity**	**Location**
9:30–17:30	Exhibition Open	Messe Frankfurt, Halls 4, 6, 8, 9, 10, and 11
9:30–17:30	Live Pharma Connect	Match & Meet Area, Hall 10.1, Stand 101C50.
10:30–17:00	Pharma Insight Briefings	Messe Frankfurt Galleria
18:00–22:30	CPhI Pharma Awards Gala	Intercontinental Hotel Frankfurt
Wednesday Oct. 25, 2017		
Time	**Activity**	**Location**
8:00–11:15	Women in Leadership Forum	Portalhaus, Frankfurt Messe
9:30–17:30	Exhibition Open	Messe Frankfurt, Halls 4, 6, 8, 9, 10, and 11
9:30–17:30	Live Pharma Connect	Match & Meet Area, Hall 10.1, Stand 101C50.
10:30–17:00	Pharma Insight Briefings	Messe Frankfurt Galleria
Thursday, Oct. 26, 2017		
Time	**Activity**	**Location**
9:30–16:00	Exhibition Open	Messe Frankfurt, Halls 4, 6, 8, 9, 10, and 11
9:30–16:00	Live Pharma Connect	Match & Meet Area, Hall 10.1, Stand 101C50.
10:30–15:40	Pharma Insight Briefings	Messe Frankfurt Galleria

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Addressing Pharma's Challenges

Presentations and panel discussions address key issues in outsourcing, manufacturing, pharmaceutical ingredients, biosimilars, generic drugs, finished drugs, and packaging.

The 9th Pre-Connect Congress provides bio/pharma executives the opportunity to explore issues impacting the future of pharma. Scheduled for Monday, Oct. 23, 2017, this congress covers the latest trends and developments in a variety of sectors through presentations and dedicated networking opportunities.

The Pre-Connect Congress will be held at the Portalhaus, Frankfurt Messe, Frankfurt, Germany. To register, visit www.cphi.com/preconnect/.

Monday, Oct. 23

9:30–10:15, **Breakfast and Networking**
10:15–10:20, **Welcome from the Chair**

CEO Industry Outlook

10:20–11:00

- Analysis of the global biomanufacturing market
- Addressing Industry uncertainty
- Creating a more comprehensive CDMO Service, driving innovation in manufacturing and reducing costs
- How can Big Pharma save CAPEX and time with more capacity flexibility?
- Supporting Biotechs in the drive for discovery and development.

Tae Han Kim, president and CEO, Samsung Biologics

Outsourcing and Manufacturing Track

11:05–11:45

Contact Manufacturing Industry Outlook

An in-depth look at the trends and developments affecting the contract manufacturing space. Gain invaluable insight and market intelligence on this sector from a leading industry influencer.

Jim Miller, president, PharmSource, A GlobalData Company

11:45–12:25

Addressing Capacity Constraints within the Contract Pharmaceutical Development Market

A significant challenge for CMOs is their ability to meet the demands of flexible scheduling and the need for capacity. This session offers an overview of current trends within the industry.

Brian Eastwood, head of business development (EU), Almac Pharma

12:25–13:15

Panel Discussion: Continuous Manufacturing

- Has continuous manufacturing reached a tipping point for future therapies?
- What can be learned from small-molecule and biomanufacturing technologies and supply chains?

Craig Johnston, industrial director, CMAC
Johnathon Marshall, partner, PwC
Massimo Bresciani, director scientific operations, Research Centre Pharmaceutical Engineering
Amina Faham, global leader–R&D pharma applications, Dow

Pharmaceutical Ingredients Track

11:05–11:50

API Sourcing & Manufacturing Update

Learn about the latest trends affecting API manufacturing and sourcing across the globe, including increased focus on innovation in countries like China and India, impact of ever-increasing regulation, changing product mix, and continued M&A activity.

Kate Kuhrt, head of GTM–Life Sciences, Clarivate Analytics

11:50–12:35

ICH Guidelines on Elemental Impurities: Strategies for Implementation

For many API and pharmaceutical product manufacturers, the implementation of ICH Q3D has a huge impact. This session will focus on understanding the methodology and developing a strategy for how a risk-based approach can be implemented.

Landry Le Chevanton, group leader, global regulatory affairs, DSM

12:35–13:15

The SPC Manufacturing Waiver: An Initiative for Stimulating R&D and Pharma Manufacturing in Europe

Price has generally dictated that pharma manufacturing takes place outside Europe, but increasing concerns over quality have stimulated discussions about reshoring. What is the potential of manufacturing returning to Europe? Could new legislation such as the Supplementary Protection Certificate Manufacturing waiver stimulate production in the EU?

Sergio Napolitano, director, legal and external relations, Medicines for Europe

13:15–14:00, **Lunch**

Bio and Generics Track

14:00–14:40

The Future of Generics: Moving from Volume to Value

Generics are the answer to creating sustainable healthcare systems in many markets, and future development of the industry looks positive despite the challenges posed from biological therapies, pricing, and the patent cliff. What is the outlook for the industry? Which markets offer new opportunities? How do generics companies need to adapt to remain profitable?

Alan Sheppard, principal—global head generics, thought leadership, QuintilesIMS

14:40–15:30

Biosimilar Uptake in the US and Europe: What Are the Current Obstacles and Opportunities?

Biosimilars present an opportunity for delivering high-value therapeutics at a lower cost, creating more sustainable healthcare systems. Despite this, adoption in the United States has been slower than anticipated, with challenges surrounding regulation

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and IP protection. This session will examine what has been stalling uptake of these products and will ask what lessons can be learned from the comparatively successful European market.
Moderator: Duncan Emerton, senior director, syndicated insights and analysis, FirstWord (pending confirmation)
Panellists:
Florian Turk, head, global payor marketing, sales and relations, Sandoz Biopharmaceuticals
Steinar Madsen, medical director, Norwegian Medicines Agency (pending confirmation)
Other panelists to be confirmed

15:30–16:15
Roundtable Discussion: Meeting Patient Needs through Innovative Therapies: CRISPR, Immunotherapy, and Personalised Medicines
Pharma companies need a more sophisticated armoury for dealing with chronic or complex disease and a wave of personalised, targeted therapies are now in development. While this holds the potential to improve patient outcomes, particularly in oncology, these therapies come with long and complex development times, target smaller patient populations, and carry huge cost implications for authorities.
Moderator: Peter Hofland, executive editor, InPress Media Group LLC
Panellists: Jeffrey Waldon, executive director, PM Connective
Hui Li, vice-president of business development and general manager of China Operations at Sorrento

FDF and Packaging Track

14:00–14:45
Growing Patient Adherence through Smart and Smarter Packaging
Developing and growing levels of patient adherence is one of the significant challenges that the Pharma industry and associated payers face today. Inadequate patient adherence results in sub-optimal patient outcomes and costs the world economy hundreds of billions of dollars annually. Smart packaging system capability and infrastructure has grown significantly and when applied can grow adherence levels in a cost-effective manner. This session will look at the opportunities and future trends in this exciting industry sector.
Chris Waterhouse, managing director, iDi Pac Ltd and chairman of the board, The Packaging Society

14:45–15:30
Serialisation Case Study: Moving from Theory to Practice
While many Big Pharma companies have an established serialization strategy in place for the November 2017 deadline, several SMEs with fewer resources are struggling to reach compliance. This practical case study session will enable you to hear from a CDMO who is already prepared and will discuss challenges encountered and lessons learned.
Daniela Geiger, Product and Service Manager, Vetter Pharma International GmbH

15:30–16:15
FDF Opportunities in China
This session will focus on market entry strategy for finished dosage exports to China. Gain insights into the Chinese pharma market, recent China Food and Drug Administration reforms, and the impact new regulations and policies will have on international companies.
Guo Xiaodan, deputy secretary of sub-chamber, FDF, China Chamber of Commerce for Import & Export of Medicines and Health Products

16:15–16:35, **Coffee Break**

Panel Discussion

16:35–17:35
Pharma Trend Forecasting: Where is Pharma Headed in the Next 10 Years?
- Trump, Brexit, and Beyond: Geopolitical challenges and influences affecting Pharma
- Digital horizons for Pharma: Technology meets medicine
- M&A and industry consolidation
- Regulatory review and outlook
- Drug pricing tension and controversies

Moderator: Rita Peters, editorial director, Pharmaceutical Technology
Panellists:
Adrian van den Hoven, director general, Medicines for Europe
Johnathon Marshall, partner, PwC
Francois Scheffler, vice-president global segment management, Pharma Solutions & Human Nutrition, BASF
Speaker from QuintilesIMS to be announced

Regulatory Keynote

17:35-18:15
Warning Letters, Approvals and Business Disruption—Is Mutual Recognition of Factory Inspections the Answer?
Analysis of the US and EU announcement to mutually recognise one another's pharmaceutical manufacturing inspection procedure: Does this hold the potential to streamline factory inspections? There is an urgent need to reduce regulator heterogeneity in the CGMP inspection process; mutual recognition of inspections is a step in the right direction but may be insufficient to address the need for harmonization. To ensure objective risk assessment and achieving consensus on risk-based enforcement actions, could common certification be considered?
Ajaz Hussain, president, National Institute for Pharmaceutical Technology & Education, Inc.; founder, Insight, Advice & Solutions LLC; and former deputy director, Office for Pharmaceutical Studies, FDA

18:50–19:00
Drinks Reception and Networking

Note: All speakers are confirmed unless indicated otherwise. Information as available on Aug. 31, 2017.

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CPhI worldwide

9th Pre-Connect Congress

October 23, 2017 | Portalhaus, Frankfurt Messe

Explore the Future of Pharma

VIEW THE AGENDA:

http://gotocphi.com/pre-connect-agenda

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Five Exhibitions in One

CPhI and co-located events offer a global marketplace of suppliers of products and services for drug development, manufacturing, and distribution.

More than 42,000 senior pharma professionals from 150 countries are expected to visit the exhibition halls of CPhI Worldwide and its co-located events: ICSE, P-PMEC, FDF, and InnoPack.

The exhibits are arranged in 20 dedicated zones covering ingredients, APIs, excipients, finished dosage, contract services, packaging, machinery, and more.

The facility floorplan on page CPhI 10 provides an overview of all exhibit hall locations. For detailed floor plans of each exhibit hall, see www.cphi.com/europe/exhibit/venue-floor-plans-cphi-worldwide.

CPhI Worldwide

CPhI Worldwide exhibits are arranged in product category zones:

- APIs: Halls 8, 9.2, 10.1, 10.3, 11.1
- Biopharmaceuticals: Hall 10.1
- Custom Manufacturing: Hall 11.1
- Excipients: Hall 10.2
- Fine Chemicals and Intermediates: Hall 10.3
- Integrated Pharma: Halls 6.0, 6.1, 6.2
- Natural Extracts: Hall 10.1
- North American Pavilion: Hall 10.2

ICSE: Contract Services

Outsourcing solution providers that offer clinical trials, contract research, contract manufacturing, biotech, IT, analytical services, packaging, and logistics services are showcased in the ICSE exhibition in Exhibit Halls 4.0, 4.1, and 4.2. Zones are defined for:

- Analytical and Lab Services: Hall 4.0
- CRO and Clinical Trials: Hall 4.1
- General Floor: Halls 4.0, 4.1 and 4.2
- Logistics and Cold Chain: Hall 4.0
- New Exhibitors: Hall 4.1
- North America: Hall 4.1

InnoPack: Pharmaceutical Packaging and Drug Delivery Systems

InnoPack, located in Hall 4.2, features a labelling zone, products and services for primary, secondary, and tertiary packaging industries, as well as drug-delivery system suppliers.

SMOKE: ANTHONY BRADSHAW/GETTY IMAGES

CPhI Exhibition Hours

Tuesday, Oct. 24, 2017: 9:30–17:30
Wednesday, Oct. 25, 2017: 9:30–17:30
Thursday, Oct. 26, 2017: 9:30–16:00

Finished Dosage Formulations (FDF)

FDF in Halls 9.0, 9.1, and 9.2 targets the formulation supply chain including pharma, contract manufacturing, out-licensing specialists, end product distributors, and generic-drug pharma companies. Solid dose, semi-solids, liquids, sprays, and sterile forms including tablets, capsules, gels, parenteral drugs, vials, patches, creams, inhalation, nasal, sublingual, and suppository forms are represented.

P-MEC

Located in Hall 4.0, P-MEC features pharmaceutical machinery and equipment. Zones are defined for LABWorld and Clean Room technology.

Exhibition Special Events

Innovation Gallery

The Innovation Gallery provides a platform for exhibitors to display innovations and new product introductions. There are two locations:

- ICSE and InnoPack Gallery in Hall 4.2
- CPhI and FDF Gallery in Galleria, between Halls 8 and 9.

For more information, visit gotocphi.com/agenda.

Innovation Tours

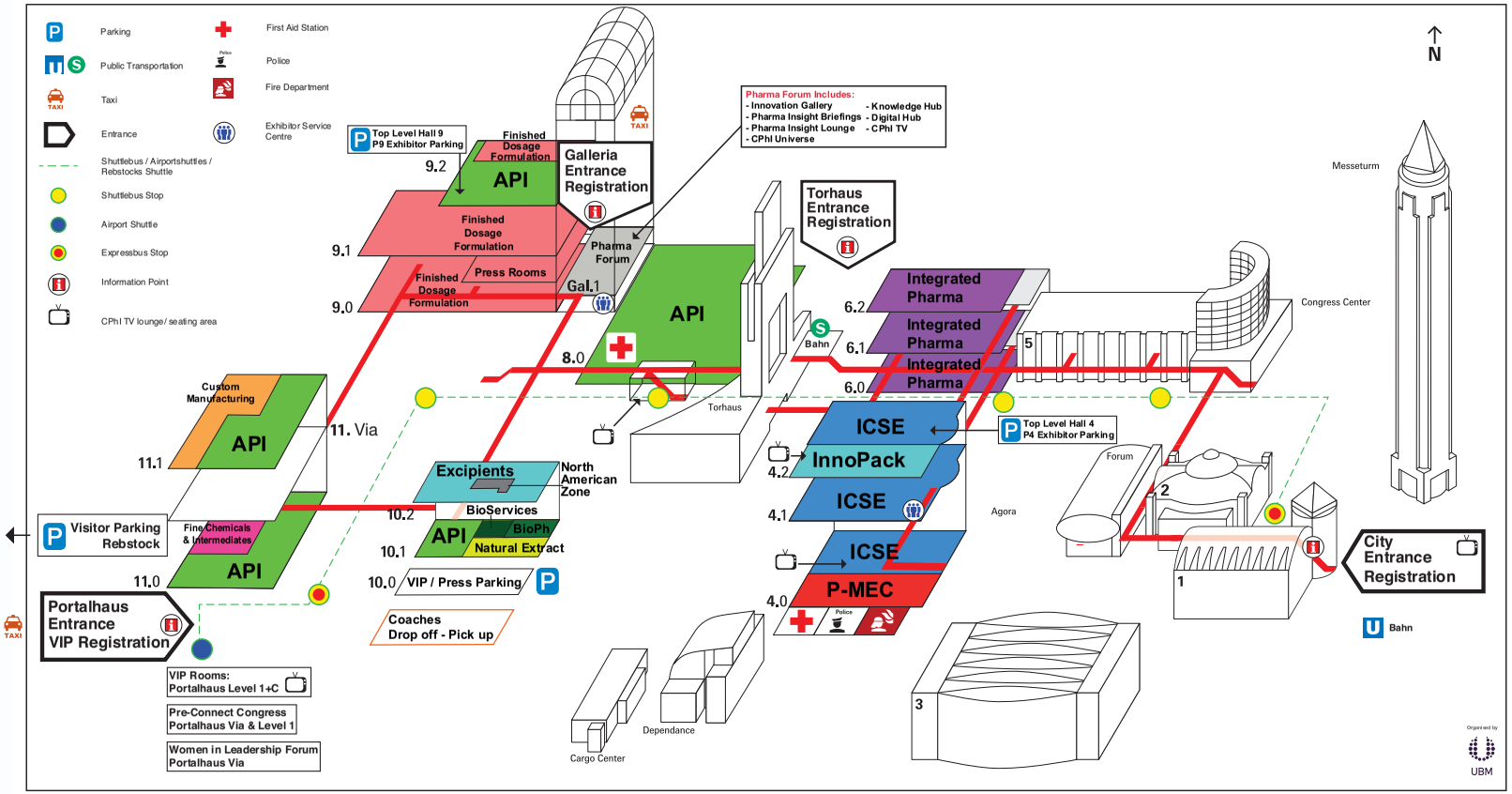
Innovation Tours bring visitors to new technologies and trends on display in the exhibit halls. The planned, 60-minute tours cover the scope of pharmaceutical development and manufacturing in the CPhI, ICSE, and InnoPack exhibits. For more information, visit cphi.com/europe/innovation-gallery.

Visitors can attend all co-located events—CPhI, ICSE, InnoPack, FDF, and P-Mec—with one exhibition pass.

CPhI worldwide
24 - 26 October 2017 Frankfurt, Germany

iCSE pharma contract services · P-mec · InnoPack · FDF

Organised by UBM



SMOKE: ANTHONY BRADSHAW/GETTY IMAGES

Featured Exhibitors

Be sure to visit the following companies exhibiting at CPhI Worldwide.

AbbVie
www.abbviecontractmfg.com
Stand # 41M11

Alcami
www.alcaminow.com/
Stand # 111F20

Catalent Pharma Solutions
www.catalent.com
Stand # 41G10

Corden Pharma
www.cordenpharma.com
Stand # 60A40

Emergent
www.emergentbiosolutions.com
Stand # 41B67

Hermes Pharma
www.hermes-pharma.com
Stand # 80H51

Jost Chemical Co.
www.jostchemical.com
Stand # 80R11

Lonza
www.lonza.com
Stand # 111C30

Marken
www.marken.com
Stand # 41K32

Nemera
www.nemera.net
Stand # 42D40

Panreac AppliChem
www.itwreagents.com
Stand # 102G43

Patheon
www.patheon.com
Stand # 41 C10

Procaps SA
www.procapslaboratorios.com
Stand # 61D10

Rommelag CMO
www.rommelag.com
Stand # 40D20

Sartorius
www.sartorius.com
Stand # 40L22

Servier CDMO
www.servier-cdmo.com
Stand # 41C50

Thermo Fisher Scientific
www.thermoscientific.com
Stand # 40K22

Unither Pharmaceuticals
www.unither-pharma.com
Stand # 41C80

Gain Pharma Insight, In Brief

CPhI Worldwide participants can stay current on the latest trends in technologies, ingredients, manufacturing and packaging practices, and business strategies.

Pharma decision makers rely on expert insight on a range of pharma industry topics to guide them when developing technical and business strategies. Visitors to CPhI Worldwide will have the opportunity to hear experts share insights, opinions, and technical updates in the Pharma Insight Briefings. These free, 30-minute presentations cover the bio/pharmaceutical development, manufacturing, distribution, and business continuum. Topics include bioavailablity enhancement, lipid formulations, capsule dosage forms, inhalation drugs, highly potent APIs, serialisation, mergers and acquisitions, regulatory issues, stability studies, risk mitigation, and more.

More than 80 commercial and technical sessions will be offered during the three days of CPhI Worldwide. The Pharma Insight Briefings will be held in three theatres in the Galeria at Frankfurt Messe.

The information below lists session and speaker information as of Aug. 30, 2017. For updates, visit www.cphi.com/europe/agenda/pibs.

Pharma Insight Briefings

Tuesday, Oct. 24, 2017: 10:30–17:00
Wednesday, Oct. 25, 2017: 10:30–17:00
Thursday, Oct. 26, 2017: 10:30–15:40

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MATEJ KASTELIC/SHUTTERSTOCK.COM

Expert panel revisits Pharma industry predictions

Five years on from the release of its first annual report in 2013, CPhI Worldwide reviewed the accuracy of the predictions made in past reports. Experts have previously predicted the expanded use of process analytical technology (PAT), quality by design (QbD), serialisation, green chemistry, R&D improvements, and the rise of strategic partnerships between pharma and contract development and manufacturing organizations (CDMOs). A potential hindrance to the industry, however, was the predicted rise in the number of warning letters issued by the US Food and Drug Administration (FDA).

The 2013 report predicted that the number of FDA warning letters would increase as a result of tightening regulations and a lagging industry. FDA reported a jump in the number of warning letters for pharma cGMP activities from 23 in 2012 to 58 in 2016, confirming the accuracy of this prediction.

Experts also predicted a boom in pharmaceutical R&D and improvements in development cycles, and 2014 and 2015 were stellar years for new molecular entities (NMEs) and biologics license applications (BLAs), with 41 and 45 FDA approvals, respectively. This figure, however, dropped significantly in the following year, with 22 in 2016.

PAT, QbD, and serialization have now become industry-wide practices for ensuring product quality, safety, and efficiency. Big Pharma and CDMOs are implementing continuous processing for their APIs and finished products, and the use of these technologies continues to increase. Previous reports also predicted a shift to green chemistry, route scouting, and process improvements to reduce the amount of waste produced. This trend is taking shape across the industry, the report states.

Experts also foresaw the proliferations of strategic partnerships between pharmaceutical companies and CDMOs. Mega-mergers are becoming more frequent, driven by competition to become leading and full-service providers. Examples include Lonza's acquisition of Capsugel and Thermo Fischer Scientific's announced plan to purchase Patheon in May 2017. In addition, Big Pharma has also setup co-development deals with a number of companies, particularly to develop and commercialise biologics and biosimilars.

The 2017 CPhI Annual Report features insight from 12 experts on the current and future state of the pharmaceutical industry, including manufacturing, R&D, regulations, biologics, PAT/QbD, and innovation, among many others. The report will be released in two parts, one before the show and the other during CPhI Worldwide, Oct. 24–26, 2017 in Frankfurt, Germany.

—The editors of Pharmaceutical Technology

Pharma Insight Briefings, Tuesday, Oct. 24, 2017

Information as of Aug. 30, 2017. Visit www.cphi.com/europe/agenda/pibs for updates.

Theatre G1A1	Theatre G1A2	Theatre G1A3
Tuesday, Oct. 24, 10:30		
Pharma & OTC: Entering the Most Prosperous Emerging Markets Reiner Christensen, CEO, Chameleon Pharma Consulting	**The Importance of Knowing Your Omega-3 Index: Recent Findings and Implications on Public Health** Andreas Berg Storsve, Director Research and Development, AkerBioMarine	**Setting New Standard for Coated Stoppers** Arnaud Fournier, business support manager, injectables, Aptar Pharma
Tuesday, Oct. 24, 11:10		
Serialisation–The Vital Role of the CDMO Erik Haeffler, vice-president, manufacturing services, Recipharm	**Applications of Plant Cell Cultures—From Bench to Commercial Scale** Gilbert Gorr, chief scientific officer, Phyton Biotech	**Successfully Activating Positive Behaviours of Stakeholders Involved in Vaccine Purchasing and Usage through Technological Advances** Pierre Morgon, senior advisor to the CEO, Pharmapan
Tuesday, Oct. 24, 11:50		
How Do I Standardise and Accelerate Serialization Onboarding of My CMOs? Rick Seibert, senior vice-president–global innovation and technology services, Sharp	**Novel Oxidant NaOCl • 5H2O for Organic Reactions** Tomohide Okada, senior researcher, Nippon Light Metal Co. Ltd	**Plastic Vials and Syringes with an Excellent Oxygen Barrier** Haruka Okazaki, researcher, Mitsubishi Gas Chemical Company
Tuesday, Oct. 24, 12:30		
Serialisation Readiness: Establishing the Right Strategy and Partnerships for Success Aude Cazenave, Technical Director, Aesica Pharma	**Solving the Insoluable: Innovative Solutions for Solubility Enhancement** Meinolf Brackhagen, senior TS&D scientist, Dow Corning	**Preventing Falsified Medicines from Entering the Legal EU Supply Chain** Michael Pilastro, business development manager, pharma, UPM Raflatc
Tuesday, Oct. 24, 13:10		
Model-Based Technology Selection for Bioavailability Enhancement David Lyon, director research, Capsugel	**Functional Capsule Technologies Based on Advanced Polymer Science** Ed Jule, director, pharmaceutical business development manager EMEA & India, Capsugel	**How Plastic Materials Can Help Protect Your Product and Your Patients** Steve Duckworth, global head of healthcare polymer solutions, Clariant
Tuesday, Oct. 24, 13:50		
Session to be confirmed Sirio	**A Tale of Two Medicines: Bridging the Gap Between Medicinal Marijuana and Pharmaceutical Cannabinoids** Giovanni Appendino, professor, Università del Piemonte Orientale, Faculty of Pharmacy and Indena Scientific Advisor, Indena	**How to Deliver Sterile Eye Drops with a Safer Alternative to Preservatives** Faustine Munoz, global category manager for ophthalmic, Nemera
Tuesday, Oct. 24, 14:30		
Development Manufacture of HPAPI Drug Products Throughout the Clinical Phases David O'Connell, director pharmaceutical development, PCI Pharma Services	**QbD Applied to Lipid-Based Pharmaceutical Products** Alyn McNaughton, technical director, Capsugel	**Oral Thin Films: Innovative Dosage Form for Improving Patient Compliance** Nidhi P. Sapkal, principal research coordinator, Zim Laboratories
Tuesday, Oct. 24, 15:10		
An Innovative Bioreactor System for Enhancing Vero Cell Growth Kamal A. Rashid, director, Biomanufacturing Education & Training Center and research professor at Worcester Polytechnic Institute Sponsored by Eppendorf	**Sterility Solutions for Silicone Tubing in Critical Biopharma Applications** Lise Tan-Sien-Hee, Dow Food, Pharma & Medical Solutions	**Future Pharma Manufacturing: RTU Packaging Solutions to Increase Flexibility and Increase Efficiency** Anil Busimi, global product manager, cartridges, Schott AG
Tuesday, Oct. 24, 15:50		
Microbial Fermentation Elise Mous, director–sales and marketing, Capua Bio Services	**An Approach to Process Risk Mitigation by FMEA** Michael Postlethwaite, business development manager, Bachem	**Driving Better Patient Outcomes with Connectivity** Chris Baron, associate director business development;Sai Shankar, business development director, connected devices, Aptar Pharma
Tuesday, Oct. 24, 16:30		
Centralising Stability Studies–Managing Risks Karan Bagaria, business development director, Recipharm	**Resin Solutions for Peptide Solid Phase Synthesis and Purification** Alessandra Basso, life tech manager, Purolite Life Sciences	**Session title to be confirmed** Alessandro Morandotti, product manager, OMPI Pharma, Stevanato Group

Pharma Insight Briefings, Wednesday, Oct. 25, 2017

Information as of Aug. 30, 2017. Visit www.cphi.com/europe/agenda/pibs for updates.

Theatre G1A1	Theatre G1A2	Theatre G1A3
Wednesday, Oct. 25, 10:30		
Quality by Design and Expertise: Accelerating Time to Market of Complex Oral Solid Dosage Forms Guy Vergnault, VP research & development; Lucile Kowalski, project manager, Skyepharma	**Recent M&A Trends in Pharma Manufacturing** Christoph Bieri, managing partner, Kurmann Partners	**Innovative Respiratory Solutions for Expanding Your Product Portfolio** Guenter Nadler, director business development, Aptar Pharma
Wednesday, Oct. 25, 11:10		
A Pragmatic (USP) Approach to Extractables and Leachables Evaluation for Single-Use Systems Andreas Nixdorf, business development manager, extractables and leachables testing, SGS Life Sciences	**Reinventing the CMO Business Model in Small Molecules** Lee Newton, director, commercial development, Lonza	**Breakthrough Antimicrobial Innovation: Patient Protection and Cost-Efficiency** Aurelie Furiga, technology manager, Pylote
Wednesday, Oct. 25, 11:50		
Enterprise Serialization Lessons Learned: From Concept to Execution Justin Schroeder, senior executive director of global marketing and design, PCI Pharma Services	**Key Impact of Silicone Excipients on the Skin Delivery of Corticosteroid Drugs** Virginie Caprasse, Dow Food, Pharma & Medical Solutions	**User-friendly Packaging Solutions for Moisture/Oxygen Sensitive Formulation** Ephraim Ulmer, chief executive officer, LOG Pharma Packaging
Wednesday, Oct. 25, 12:30		
See-Through Raman Identification of Incoming Materials in Pharmaceutical Warehouses Enrique Lozano Diz, business development, B&W Tek	**HPMC Capsules in Prescription Pharmaceuticals—Emerging Trends** Jnanadev Bhat, general manager–product development and new product offerings; Fernando Diez, scientific business development manager, ACG Worldwide	**Final Sterilisation for Pharmaceutical Applications: Development of Innovative Customised Solutions** Bart Croonenborghs, technical director irradiation, Sterigenics
Wednesday, Oct. 25, 13:10		
Spray Drying for Inhaled Dosage Forms David Lyon, director, research, Capsugel	**Encapsulation Tools for Rapid Feasibility Assessments to Speed Up First-In-Human Studies** Laurent Bouché, pharmaceutical project manager, Capsugel	**Emergence of Plastic Caps—Market Drivers and Key Considerations for Assessment** Sylvia Marzotko, product management & marketing, West Pharmaceutical Services
Wednesday, Oct. 25, 13:50		
Session to be confirmed	**Driving Responsible Procurement in the Pharmaceutical and Healthcare Sector** Mark Bannister, sustainable procurement regional lead, EMEA, Takeda, Sponsored by Pharmaceutical Supply Chain Initiative	**Enhanced Flexibility for Packaging Requirements: Ready-to-Fill Vials** Maximilian Vogl, product manager injection devices, Gerresheimer AG
Wednesday, Oct. 25, 14:30		
Realizing Innovative Engineering Concepts–Today, Tomorrow and Always Customer Focused Kayleigh Hearse, project manager, Baxter BioPharma Solutions	**Excipient Management for Encapsulated Products: Going Beyond the Risk Assessment Exercise** Kaat Bracquiné, senior manager, quality and regulatory affairs, Capsugel	**The End Justifies the Means: Using Dose Design & Delivery Technology to Improve Clinical and Commercial Success** Smart dose design can have a far-reaching impact on the success of a drug. Topics explored during this workshop include: • The Three Ps: Satisfying the needs of patients, prescribers, and payers in achieving a successful drug • Connecting the Dots: a review of dose technologies and best fits for patient groups and markets • Molecule in the Middle: The importance of optimising your dose form for the challenges of your API • Fast-track to Formulary: Accelerating to market and beyond by optimising scale-up, manufacturability, and CMC Catalent
Wednesday, Oct. 25, 15:10		
Contract Manufacturing Services for Pre-Filled Syringes–From Standard Solutions to Complex Products Stefan Czvitkovich, director PP sterile pharmaceuticals Central Europe, Fresenius Kabi	**Advanced Reduction Chemistry** Giovanni Papandrea, CEO, Chematek	
Wednesday, Oct. 25, 15:50		
Time to Scale Up Your API? Optimising Your Process Can Yield Huge Savings Evan Boswell, principal scientist, Pfizer CentreOne	**The Importance of Particle-Size Reduction by Milling and Micronisation on Industrial Scale** Herbert Hansen, Advisory Board, Gesellschaft für Micronisierung	
Wednesday, Oct. 25, 16:30		
QbD: A Tool to Success Jegadeesh Thampi, Syngene	**Improved Absorption and Purification of Active Pharmaceutical Compounds** Fred Ghanem, North America business manager–life sciences, Purolite Life Sciences	**Session to be confirmed** Linnea

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Pharma Insight Briefings, Thursday, Oct. 26, 2017

Information as of Aug. 30, 2017. Visit www.cphi.com/europe/agenda/pibs for updates.

Theatre G1A1	Theatre G1A2	Theatre G1A3
Thursday, Oct. 26, 10:30		
Purification of Pharmaceutical Effluents: Electrochemical Oxidation as a Universal Treatment Technology Dieter Woisetschläger, lead engineer–wastewater treatment, VTU Engineering	**Global Trends for Natural Medicine** Rajiv Khatau, director, LODAAT	**Tamper Verification Features on Medicinal Product Packaging– From Europe Across the Globe** Dieter Mößner, project engineer pharma, Edelmann
Thursday, Oct. 26, 11:10		
Session to be confirmed	**Low in Endotoxins Minerals for Pharmaceutical Applications** Jenny Barbier, head of technical marketing, Dr. Paul Lohmann	**Session to be confirmed**
Thursday, Oct. 26, 11:50		
Solutions for Serialisation of Pharmaceutical Products Kerstin Vieluf, senior technical key account manager, IDT Biologika	**Registration Insight and Pricing Structure Across the MENA Region** Yahya Al Jefri, CEO, Annahdah Medical Company	**Worth Knowing Developments in the Field of Isolator Systems** Michael Knes, sales and key account manager, Ornter
Thursday, Oct. 26, 12:30		
Session to be confirmed Verify Brand	**Biosimilars: An Evolving Market** Nicola Travierso, president, Velit	**Session to be confirmed**
Thursday, Oct. 26, 13:10		
A CDMO's Perspective: Our Role in Today's Supply Chain Marc Sauer, vice-president, R&D; Matt Frizzle, director, business development, CMO BioVectra	**Key Differences Between the New Medical Device and the OTC Regulations in Europe** Anne Laure Tardy, medical and regulatory consultant in nutrition and health sciences, RNI Conseil	**Session to be confirmed**
Thursday, Oct. 26, 13:50		
Session to be confirmed	**MENA and Latin America: Attractive Markets for New Opportunities in Innovation and Generics** Trajko Spasenovski, life sciences consultant-emerging markets, Clarivate Analytics	**Session title to be confirmed** Edwin Aret, scientific lead for the solid-state chemistry group, Alcami
Thursday, Oct. 26, 14:30		
Cell & Gene Therapies Martin Pohle, branch manager BER & LEJ, World Courier		**Session to be confirmed**
Thursday, Oct. 26, 15:10		
A Patient Centric Supply Chain—The Direct-to-Patient Value Proposition David Spillett, key account director, World Courier	**Session to be confirmed**	**Session to be confirmed**

Report: Indian Pharma companies plan expansions, improve on data integrity

A recent CPhI report on the India Pharma market revealed trends in pharma market development including business size and target markets, investment plans, and perceptions about regulatory compliance. The study, issued in August 2017, was based on opinions from 500 domestic and international companies.

About half of the responding Indian pharma companies are investing in commercial scale and scale-up facilities; approximately one-third are investing in continuous processing, and more than 20% are investing in biologics and aseptic/sterile. Over the next three years, the number of companies planning to invest in biomanufacturing facilities will rise to one third, according to the report.

The report identified a two-tier manufacturing market, one targeting Western pharma economies with generic-drug products, and the second, composed of smaller and medium-sized pharma companies, which focus on developing countries to export high-volume, low-margin generic products. The report authors anticipate consolidation in this market segment as the companies move to formulations with greater margins.

The report also highlighted that the international reputation of the country on data integrity has also improved; 96% agree that the Central Drugs Standard Control Organization (CDSCO) certification programs and initiatives are helping increase compliance. Fifty-two percent of international respondents believed the CDSCO is moving toward comparability with the standards of the European Medicines Agency and the US Food and Drug Administration.

One concern stressed by 86% of domestic companies was an overreliance on Chinese ingredients within the finished formulations sector. Additionally, 81% of domestic companies believe that the Indian government needs to urgently invest in domestic API facilities and provide tax-breaks and incentives to secure the Indian generics industry and prevent losses in market share.

—*The editors of* Pharmaceutical Technology

Recognizing Pharma Innovation

The 2017 CPhI Pharma Awards expand to 20 categories, adding recognition for patient centricity, small and large pharma companies, mHealth, export promotion, and more.

For 14 years, the CPhI Pharma Awards have recognized top innovator companies from the global bio/pharma community during the CPhI Worldwide event. In 2017, the awards programme has been expanded to include 20 categories.

The CPhI Pharma Awards are designed to raise the profile of unique innovations with key pharma professionals, the global trade press, and industry professionals.

Finalists will be announced mid-September 2017. Winners will be announced at the CPhI Pharma Awards Gala Dinner on Oct. 24, 2017 during CPhI Worldwide.

Excellence in Pharma: API Development

Innovation in technologies, products, processes, and services for the development and manufacture of active pharmaceutical ingredients (APIs) including, but not limited to, synthesis, characterization, formulation, scale-up, software and database development, and bulk manufacturing.

Excellence in Pharma: Formulation

Innovation in technologies, products, processes, and services related to the formulation of drug products including, but not limited to, excipients, novel software and databases, process development, resolving formulation challenges such as solubility/bioavailability enhancement, drug targeting or controlled release, solving stability issues such as protein aggregation, etc.

Excellence in Pharma: Excipients

Innovations in inactive pharmaceutical ingredients to improve the manufacturing process or the formulation, including, but not limited to stability, solubility, taste masking, controlled release, or other factors.

Excellence in Pharma: Manufacturing Technology and Equipment

Innovation in technologies, products, processes, and services for the manufacture of solid, semi-solid, parenteral, inhalation, or other dosage drugs including, but not limited to, equipment, manufacturing processes, facilities, process controls, and continuous manufacturing.

Excellence in Pharma: Bioprocessing

Innovation in technologies, products, processes, and services for the manufacture of biologic-based drugs including, but not limited to, equipment, raw materials, cell lines, manufacturing processes, facilities, process controls, and continuous manufacturing.

2017 CPhI Pharma Awards Gala

Tuesday, Oct. 24, 2017, 18:00–22:30
Intercontinental Hotel Frankfurt
URL: awards.cphi.com

The CPhI Pharma Awards recognize innovation in 20 categories.

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Excellence in Pharma: Analysis, Testing, and Quality Control

Innovation in technologies, products, processes, and services for the analysis and testing of drug substances, raw materials, and drug products in a laboratory on production line setting including, but not limited to, laboratory instruments and equipment, analytical instruments, laboratory software, quality control tools, data integrity systems, and contract laboratory services.

Excellence in Pharma: Drug Delivery Devices

Innovation in technologies, products, processes, and services related to delivery of drug products to patients including, but not limited to, inhalers, auto-injectors, vials, syringes, patches, and combination products.

Excellence in Pharma: Packaging

Innovation in technologies, products, processes, and services related to primary and secondary packaging for finished drug forms including, but not limited to, tamper-proof packaging, child-safety packaging, labelling, intelligent packaging, and fill/finish.

Excellence in Pharma: Supply Chain, Logistics, and Distribution

Innovation in technologies, products, processes, and services for ensuring the safe handling and tracking of drug substances, raw materials, and finished drug products including, but not limited to, logistics, cold chain, transport services, track and trace, shipping containers, and distribution channels.

Excellence in Pharma: Contract Services and Outsourcing

Innovation in contracted services and processes for the bio/pharmaceutical industry including, but not limited to, drug research, development, formulation, scale up, process development, clinical trial manufacturing, drug product manufacturing, API development and manufacturing, laboratory services, and consulting.

Excellence in Pharma: Regulatory Procedures and Compliance

Innovation in technologies, products, processes, and services designed to aid and ensure that bio/pharma companies comply with compendial standards, rules, and guidance documents established by regulatory authorities including, but not limited to, consulting services, development of consortia and industry groups, reference standards, educational programmes, and software and IT, technologies, and equipment.

Excellence in Pharma: Corporate Social Responsibility

This award recognizes innovation in improving transparency and public outreach, recognizing new programs including, but not limited to, charitable work, sustainable sourcing, environmental protection, staff reward policies, drug access schemes for patients, training/mentoring programmes, responsible sourcing, fair employee pay/ethical working policies.

Excellence in Pharma: CEO of the Year

The chief executive officer of an innovator or generic-drug company is eligible for nomination. Attributes to be considered include, but are not limited to, financial performance, product performance, global reach, leadership skills, management capability, charity initiatives, regulatory compliance, profitability, vision, marketing, acquisitions, corporate strategy, and financing. Note: This category is limited to bio/pharma companies.

Excellence in Pharma: Pharma Company of the Year–Large

This category is open to any large bio/pharmaceutical company that develops, produces, and markets drugs or pharmaceuticals. We define a large company as one with over 250 employees.

Excellence in Pharma: Pharma Company of the Year–SME

This category is open to any small and medium-sized (SME) bio/pharmaceutical company that develops, produces, and markets drugs or (bio) pharmaceuticals. We define a SME company as one with up to 249 employees.

CPhI Pharma Award winners are announced and recognized at an awards gala.

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Excellence in Pharma: Sustainability Initiative of the Year

This category recognizes sustainable development in the pharmaceutical industry through innovative and sustainable use of resources and prioritizes the needs of the wider environment and society.

Excellence in Pharma: Export Promotion

This category recognizes pharma companies that has seen a significant growth in export turnover year-on-year in % terms.

Excellence in Pharma: OTC

This category recognizes the process of developing the drug, but not the properties of a drug product. The category is limited to drug products that are subject to regulatory review.

Excellence in Pharma: Patient Centricity

Innovation in technologies, products, processes, and services related delivery of drug products to patients. But this category especially recognizes the attention and care for improved patient wellbeing.

Excellence in Pharma: IT, mHealth & Digitilisation

This category recognizes pharma companies that are making steps toward offering a range of services that support patient compliance, adherence, or interdisciplinary collaboration. But also innovations like measuring the real-life effects of medicines or fully integrated services that will improve the quality and efficiency of care.

For more information about the CPhI Pharma Awards, visit awards.cphi.com.

CPhI 2017 Registration and Travel

Frankfurt, Germany is host to the 2017 CPhI Worldwide event. The following location, transportation, registration, and travel information can assist visitors in planning their time at CPhI.

Location

Messe Frankfurt is located at Ludwig-Erhard-Anlage Frankfurt, Germany. The facility is accessible by taxi, automobile, suburban, and underground train lines. Parking is available onsite. Transportation details can be found at www.messefrankfurt.com.

The following entrances to the venue will be in use for visitor registration during the exhibition:

- City Entrance
- Torhaus Entrance: close to Halls 4, 6, and 8
- Galleria Entrance: close to Halls 8 and 9
- Portalhaus Entrance: close to Halls 10 and 11

Exhibition hours

Oct. 24, 2017: 9:30–17:30
Oct. 25, 2017: 9:30–17:30
Oct. 26, 2017: 9:30–16:00

Registration

Registration provides access to CPhI and co-located exhibitions ICSE, P-MEC,FDF and InnoPack, as well as prearranged meetings with exhibitors at exhibitors'stands or the Live Pharma Connect Stand.

Visitor registration is free of charge until Oct. 15, 2017 midnight (GMT+1), a fee €140 is applicable afterwards.

The upgraded VIP package includes access to the VIP lounge, fast track entry, a dedicated cloakroom, and access to the Exhibitor and VIP party. The Exclusive VIP package includes the basic and VIP offerings, plus access to the Pre-Connect Congress, a daily lunch voucher, and entrace to the CPhI Pharma Awards Gala and Dinner.

Visit www.cphi.com/europe/visit/packages-and-prices for details.

No one under 18 years of age will be admitted.

Travel Arrangements

Hotels: b network, the official accommodation agency for CPhI in 2017, has secured a range of accommodation solutions at different price points and can assist with accommodation bookings at more than 60 properties in the Frankfurt area.

Air Travel: SkyTeam is the Official Alliance Network for air travel to CPhI, offers travel savings up to 15%, reward miles, and other services.

Visas: CPhI can provide Visa application assistance to visitors from China and other countries in Asia.

See www.cphi.com/europe/visit/travel-information-2 for travel information and details.

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SRDJAN DRASKOVIC/SHUTTERSTOCK.COM

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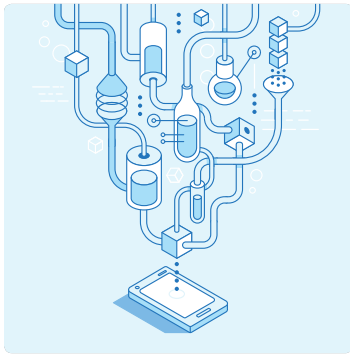
Applying QbD in Process Development

Andrew Anderson, Graham A. McGibbon, and Sanjivanjit K. Bhal



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Informatics software can be used to address the challenges of quality by design, such as managing impurity data when developing an impurity control strategy.

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Over the past few years, global regulatory authorities have been raising the expectation of incorporating quality by design (QbD) into pharmaceutical development. While QbD offers many important long-term benefits, these expectations are having a dramatic impact on product development groups and their supporting corporate informatics infrastructure. This article discusses how QbD requirements for risk assessment, process assessment, material assessment, documentation, and traceability can be addressed with informatics, using development of an impurity control strategy as an example.

QbD in process development

One of the major impacts of using QbD principles in process development is the requirement to establish an acceptable quality target product profile (QTPP). Establishing the QTPP is accomplished through:

- Evaluation of input material quality attributes (MQA)
- Evaluation of the quality impact of critical process parameters (CPP)
- Consolidated evaluation of every MQA and CPP for all input materials and unit operations.

MQA assessment requires the careful consideration of input materials to ensure that their physical/(bio)chemical properties or characteristics are within appropriate limits, ranges, or distributions. Furthermore, for CPP assessment, unit operation process parameter ranges must be evaluated to determine the impact of parameter variability on product quality. The contribution of each unit operation in any pharmaceutical or biopharmaceutical manufacturing process—whether it be synthetic steps in a chemical process (e.g., filtering, stirring, agitating, heating, chilling) or product formulation (e.g., impurity control) must be assessed.

Challenges in impurity control

Impurity control strategy development is an example of this iterative evaluation process. For regulatory submission of a substance or product under development, information from many activities is necessary to complete the quality module of a common technical document (CTD or eCTD).

Initially, chemical structure information may be available from chemists' individual electronic laboratory notebooks, but the affiliated unit operation details and the complete supporting molecular characterization data are not usually directly available. Moreover, some of that data and interpreted information may

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have been transcribed into Microsoft Excel spreadsheets. In the authors' informal survey of pharmaceutical development groups, the majority of project groups were found to be managing these data with Microsoft Excel. In those Excel spreadsheets, synthetic process and supporting analytical and chromatographic data are abstracted to numbers, text, and images, and the raw data are stored in archives. Project team members spend many hours transcribing complex and repetitive data from various systems into complex spreadsheets in an effort to harmonize the most necessary information into a single environment. Because Excel was not designed to handle chemical structures and associated scientific data, separate reports are still needed to assemble subsets of analytical characterization information and interpretations. The analytical information is transposed for decision-making purposes, but a review of the decision-supporting data is, at best, impractical because it has been sequestered into different systems. Batch-to-batch comparison data are also transcribed into the same spreadsheets in an attempt to create a central repository of information. Project teams spend weeks on the assembly of this information for internal reporting and external submissions. This abstracted and repeatedly transcribed information is then reviewed to establish and implement control strategies in compliance with a QbD approach.

The challenge for product development project teams is to not only plan and conduct the process experiments unit operations, but to acquire, analyze, and then most importantly, to assemble and interpret the various data from analysis of input materials and process information. Since the development process is iterative, all the salient data must be captured and dynamically consolidated as process operations are conducted to enable facile review of the information for ongoing risk assessment of impurities.

Concurrently, test method development must be performed to demonstrate robust capability for detection of the complete impurity profile, which includes any significant known or potential impurities from each process. Currently, control strategies rely on unrelated instruments and systems to acquire, analyze, and summarize impurity profile data and interpretations made during process route development and optimization.

Collating information for an impurity control strategy

To establish effective process and analytical impurity control strategies, a comprehensive set of information must be collated. One of the biggest challenges is that the relevant types of information, data, and knowledge required exist in disparate systems and formats. These data include:

- Chemical or biological substance information: chemical structures or sequence information
- Process information: unit operation conditions, materials used, location, equipment information, operator identification, suitable references to operating procedures and training, and calibration records
- Unit-operation-specific molecular composition characterization data: spectral and chromatographic data collected to identify and characterize compounds and mixtures (hyphenated liquid chromatography techniques, mass spectrometry, nuclear magnetic resonance, and optical techniques)
- Composition differences in materials between specific unit operations and across all unit operations
- Comparative information for each batch for a single "process", which is a single set of unit operations that are employed to produce a product or substance
- Comparative information for any or all employed processes.

To effectively establish control strategies in accordance with these collation requirements, users need the ability to simply aggregate all of the information, data, and knowledge in a single, integrated, and interoperable platform. Moreover, such informatics platforms should allow for direct data integration: the data streaming from their respective sources are automatically imported, processed, interpreted, stored, and made readily accessible. These integrations to the platform should optimally be conducted with as little human intervention as possible. Data sources relevant to impurity control strategies include analytical instrumentation, electronic laboratory notebooks, substance registry/inventory management systems, and laboratory information management systems (LIMS), particularly the work request portion of LIMS functionality.

Within the informatics platforms, users must be able to search, review, and update the information on a continual basis as projects progress and evolve. Data access should support sharing of data for collaborative research while protecting data integrity.

Using process maps

Additionally, informatics platforms should optimally provide users with the ability to construct process maps that allow visual comparison of molecular composition across unit operations. This visual comparison allows users to rapidly identify where in a process appropriate impurity control measures need to be put in place to assure effective and efficient process control. The platform should also allow the user to visualize the wide variety of related spectroscopic and chromatographic data in a single environment for each stage and substance. Such analytical data allows users to visually confirm the veracity of numerical or textual interpretations or processed results without having to open separate applications. The platform should also store the context of the experiment, expert interpretation, and decisions resulting from it. Dynamic visualization of this assembled and aggregated information preserves data integrity while supporting decision-making. Some examples of decisions that can be made more efficiently using informatics include:

- Risk assessment conclusions pertaining to impurity onset, fate, and purge
- Comparative assessments of different purification methods
- Comparative assessments of different control strategies.

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Why Bottles with Desiccant Outperform Foil-Foil Blister Packaging

Kenneth C. Waterman, Stephane Rault, Valere Logel, Aurelie Emond, and Mark Florez

IMAGE COURTESY OF CLARIANT HEALTHCARE PACKAGING

Many solid drug and consumer products, especially tablets and capsules, show moisture sensitivity that can be quantified using specialized stability studies that encompass the moisture-modified Arrhenius equation combined with an isoconversion calculation (e.g., ASAPprime, FreeThink Technologies, Inc.). While cold-form, foil-foil (aluminum-aluminum) blister packaging is considered the most moisture-protective packaging available, in fact, plastic containers such as bottles and tubes, when combined with desiccants, such as silica gel canisters and packets, will often provide lower internal relative humidity for long time periods. This in turn can result in greater stabilization of the product and a longer assignable product shelf-life.

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Most health-related products have an expiration date (shelf-life) determined based on chemical and physical changes in product attributes over time. For regulated products such as pharmaceuticals (prescription or over the counter) and nutraceuticals (including vitamins), this stability-indicating change is most often either an increase in the level of degradation products or a decrease in potency of the active(s) due to chemical degradation. Less often, the shelf-life is limited by changes in dissolution properties for solid products, such as capsules and tablets. Whatever the shelf-life limiting attribute, changes are commonly affected by temperature, relative humidity (RH), and oxygen level. These attributes are in turn impacted by the initial drug product water content, the storage conditions, and the moisture and oxygen permeability of the packaging.

The Accelerated Stability Assessment Program (ASAP) involves a series of designed conditions of temperature and RH that samples are exposed to without packaging in order to build a stability model of a product. The data are first used to determine the failure times at each conditions (isoconversion times), then these times are fit to the moisture-modified Arrhenius equation to determine the explicit temperature and RH sensitivity (B-term). The design and analyses are conveniently carried out using commercial software (e.g., ASAPprime, FreeThink Technologies, Inc.). In this modeling, the RH sensitivity of products follows an exponential function (with the exponent B). From an ASAP model of a product's degradation behavior, it is possible to accurately determine the product's shelf-life at different storage (i.e., combination of temperature and RH) and packaging conditions. For products that have a significant moisture sensitivity (i.e., a high B term found from the ASAP study), protection from moisture by packaging is an effective method of increasing the stability.

Packaging for moisture-sensitive products

For blister packaging, the most protective packaging is cold-form, aluminum-aluminum (alu-alu) blisters. In this case,

the moisture permeability (moisture vapor transmission rate [MVTR]) is virtually zero. As such, foil-foil packaging is often considered the "gold-standard" for protection of moisture-sensitive products. Interestingly enough, using moisture-permeable bottles (e.g., those made from high-density polyethylene [HDPE] or multilayer bottles) can actually provide greater stabilization for moisture-sensitive products. The key to this is the use of desiccants. Such desiccants are available in various configurations, the most common of which are the automatable drop-in form canisters and packets (e.g., Sorbit, Clariant), but can also include desiccant closures and protective systems such as tubes and desiccant stoppers.

Figure 1: Calculated internal relative humidity (%RH) and loss of active as a function of storage time for storage at 30 °C/75%RH (zone IVB) for three types of packaging: cold-form blisters (alu-alu), 60-cc high density polyethylene (HDPE) bottles with heat induction seal (HIS) caps containing 30 tablets, and the same bottles containing 2 g of silica gel desiccant. Tablets are composed of 100 mg thiamine (vitamin B1), 150 mg microcrystalline cellulose, 75 mg lactose, 20 mg croscarmellose sodium, and 5 mg magnesium stearate. The initial RH (water activity) of the tablets is assumed to be 35% (water activity 0.35).

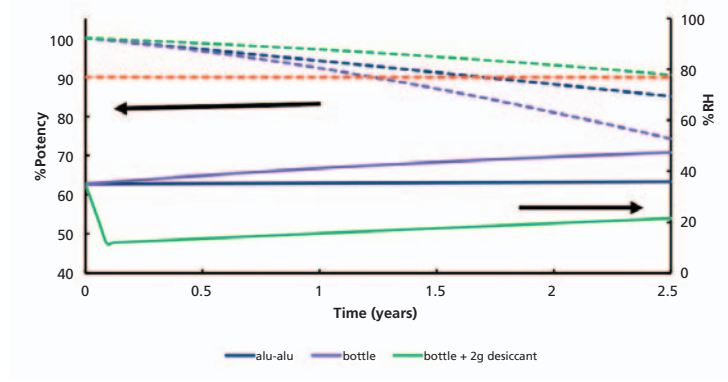

FIGURE COURTESY OF THE AUTHORS.

Moisture sorption and relative humidity

To understand why this is the case, it is important to first understand how moisture distributes within a package, then how moisture transfer affects the RH inside the package over time. Moisture is held by solids to a different degree depending on the RH of the environment. Moisture sorption involves both water bound to the surface of solids (adsorption) and water within a matrix itself (absorption). This behavior is described by the moisture sorption isotherm of the product. Sorption isotherms are commonly measured using dynamic vapor sorption (DVS) instruments, which measure the weight gain/loss as a function of RH. With crystalline materials, virtually all the water is bound on the surface. The result is that relatively little water can sorb to these materials, even at high RH conditions. With amorphous materials, significantly more water can sorb within the solid matrix. Mixtures of materials, even processed into tablets, behave as a weighted average of the individual materials.

Inside a bottle or blister, the moisture in the headspace and the solids equilibrate relatively quickly (minutes for powders to hours for film-coated tablets). This equilibration means that the solids will gain or lose water to bring the RH of the solid (water activity) equal to the RH in the headspace. Because the solids typically hold far more moisture than the headspace, the RH of the solids will normally dominate where that equilibrium lies. The RH of the solids will depend on preparation and storage conditions prior to packaging. Most often, this RH will vary between approximately 20 and 50% RH. In many applications, companies set specifications for water content rather than water activity. Water content can be converted to water activity using the moisture sorption isotherm and correcting for any water of hydration.

Foil-foil blister versus bottles with desiccant

Moisture will transfer into a package (assuming a higher RH external than internal) at a rate proportional to the difference in RH between the external and internal environments. This proportionality constant is called the moisture vapor transmission rate (MVTR). The MVTR of foil-foil blisters is low because water vapor only permeates through the seal layer and not through the metal substrate. This means that during a two-year period, the RH inside the foil-foil blister will remain almost unchanged.

In contrast, the MVTR of plastic bottles (such as those made from HDPE) is related to the wall thickness and overall surface area due to the permeable nature of plastics. For a given bottle size, an amount of water will enter and re-equilibrate between the headspace and the solids. This means that the greater the sorption capacity of the solids (based on the sorption isotherm and mass), the slower the RH will increase. As temperature increases, the MVTR also increases.

Case study example

Figure 1 shows the RH as a function of time for a typical tablet product in alu-alu blisters, in 60-cc HDPE bottles (with heat induction seals), and with the bottles containing 2 g of silica gel desiccant, all stored at 30 °C/75% RH (International Council for Harmonisation Zone IVB conditions). As can be seen, the RH starts the same for the three packaging configurations, but in permeable bottles without a desiccant, RH increases over time, leading to lower stability of the tablets.

A desiccant is a material that can absorb a significant amount of moisture for its weight. The most common desiccant used commercially is

silica gel, but molecular sieves and desiccants combined with activated carbon are also common. Typically, silica gel desiccants are provided with their moisture levels before insertion into packaging at a low value and comply with the new *United States Pharmacopeia* (*USP*) <670>. When a desiccant is added to a bottle containing solids, the moisture will transfer between the solids, the desiccant, and the headspace until all reach an equilibrium at the same RH (water activity). Because the RH of the desiccant is generally lower than the drug products, the drug products will lose water to the silica gel. This means that the solid will rapidly equilibrate to an RH below that for the solid that is directly packaged without the desiccant. As moisture transfers into the bottle with desiccant, the rate of RH increase will be buffered by the sorption capacity of the desiccant. As shown in the example in **Figure 1**, even after two years' storage at 30 °C/75% RH, the internal RH in the bottle remains below that for the alu-alu blister. The ability of desiccants to remove water from the solid-dosage form is a unique benefit of using desiccants that cannot be matched even using impermeable alu-alu blisters.

From ASAP studies, it is possible to determine the explicit humidity sensitivity of a product, which can be combined with the knowledge of the RH as a function of time inside the package to determine the product's shelf-life in any package with known permeability (MVTR). As an example, an ASAP analysis of thiamine (vitamin B1) in a multivitamin tablet showed that this active has about an average moisture sensitivity for loss of the active (B equals 0.036). As shown in **Figure 1**, the product's estimated shelf-life (in this case for storage at 30 °C/75% RH) in HDPE bottles based on the RH curve discussed above is only 1.2 years. This improves to 1.7 years in alu-alu blisters. With 2 g of silica gel desiccant in the bottle, the shelf-life increases to 2.6 years. As a note, in polyvinyl chloride, PVC, blisters, the shelf-life is only 0.5 years (not shown). In this example, only with the desiccant is the shelf-life greater than two years.

For any specific product, it will be important to carry out an ASAP study to determine the product's exact moisture sensitivity. In many cases, the greatest shelf-life will be achieved not with impermeable, alu-alu blister packaging, but rather with bottles or other types of packaging (e.g., tubes) containing desiccants. **PT**

Process Development — *contin. from page s30*

Preserving context

To preserve the rich scientific information stored in the database, an informatics system should limit the need for data abstraction. Data abstraction in analytical chemistry is the process whereby spectral and chromatographic data are reduced from interactive data to images, text, and numbers that describe and summarize results. Although data abstraction serves a purpose—reduction of voluminous data to pieces of knowledge—it also brings limitations because important details, knowledge, and contextual information can be lost. An example of data abstraction, and its inherent risks, is identity specification and testing. One of the classic standards of identity is that a spectrum obtained for any batch of a substance matches the reference standard of the same substance. The specification can at times be limited to, for example, a set of "diagnostic" spectral features. As such, these spectral features can be abstracted to a discrete set of numerical values. Such abstraction, however, presents some discrete risk. For example, should unanticipated spectral features not accounted for in the specification be present in a spectrum for an adulterated substance, that substance would pass an identity test (i.e., expected peaks are found and the substance passes while unexpected peaks representing a new impurity are not accounted for).

Informatics strategies

Cross-functional development project teams, comprised of representatives from the various groups and departments that generate the data and make decisions from it, spend many hours sourcing and assembling the necessary information for impurity control. For each process iteration, effort is needed to acquire and evaluate new data, to perform new interpretations and identifications, and eventually to reassess the variance in impurity profiles for each process and across all processes. One of the major challenges is that while spreadsheets tend to be quite effective for handling numbers and relating them in certain specified ways to calculate values (e.g., sums and averages) and make simple graphs, they are not effective at handling and relating chemical structures with the analytical spectra and chromatograms used to identify them. An informatics system dynamically relates chemical and analytical data, results information including variances, and the interpretation knowledge from both computer algorithms and scientists, to improve productivity.

Conclusion

Many hours are often spent sourcing and assembling the necessary information for impurity control. Spreadsheets, though useful for handling mathematical and statistical data, are not capable of relating chemical structures with the analytical spectra and chromatograms used to identify them. An informatics system, on the other hand, can relate chemical and analytical data, including variances, and interpretation knowledge. **PT**

How to Get the Most from Regulatory Outsourcing

Bettina Goldberg, Philip Smith, and Joanne Sullivan

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Regulatory outsourcing can result in improved compliance, greater transparency, higher productivity, increased cost-effectiveness, and desired strategic outcomes.

Bettina Goldberg is vice-president, Clinical Trials Regulatory Services; **Philip Smith** is senior director, Integrated Product Development; and **Joanne Sullivan** is corporate vice-president, Regulatory Outsourcing Services, all at PAREXEL Consulting.

The pharmaceutical industry's return on investment (ROI), and the number of new products in its pipeline, has been decreasing for decades. To cut costs and increase efficiency, many pharma companies embraced outsourcing. Clinical operations, product formulation, and manufacturing were the first functions to be outsourced.

But outsourcing of regulatory support has been perceived by many companies as an unacceptable risk; a failure to win marketing approval or maintain compliance for a product can cause significant harm (e.g., delayed or lost income, reduced market share, or reputational damage).

If properly governed, however, regulatory outsourcing can result in improved compliance, greater transparency, higher productivity, increased cost-effectiveness, and desired strategic outcomes. And the risks have become manageable.

Today, regulatory outsourcing is becoming more desirable for more companies, due to:

- Increasingly complex approval and post-approval requirements across the globe
- New global data and format requirements (identification of medicinal products [IDMP], electronic Common Technical Document [eCTD], etc.)
- Pressure for shorter development timelines from investors and other stakeholders
- Rapidly changing national, regional, and local guidelines and statutes that are difficult to monitor and respond to.

Outsourcing, which offers a flexible workforce, can smooth uneven and unpredictable aspects of regulatory workloads characterized by periods of intense activity—such as clinical trial applications, marketing applications, and compliance crises—followed by relatively quiet times involving routine, but critical, maintenance filings. Smaller firms are challenged to maintain underutilized resources during slow times while larger firms that can afford to employ sufficient compliance teams are reluctant to do so as other investments, such as R&D or mergers and acquisitions, may have a better ROI.

In a survey of regulatory executives from international pharmaceutical firms in five European Union countries,

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A Q&A

Smaller Biotech Companies and the Single-Source CDMO

The benefits of single-source networks to smaller innovator companies.

A single-source CDMO that manages the end-to-end relationship with pharmaceutical or biopharmaceutical clients can bring many benefits and efficiencies to the development process. However, smaller companies, in particular, may still be reluctant to work with a much larger, single-source vendor. Expanding upon the discussion started at a panel featured at CPhI North America 2017, *PharmTech* speaks with Doug Johnson, PhD, founder of OCAM Solutions, about these important issues.

Pharmaceutical Technology: During the panel discussion at CPhI North America, you stated that the value of the single-vendor model is increasing. How so?

Johnson: How vendors have developed competencies has changed over time. More recently, single-source contractors have been expanding by acquiring very competent companies rather than by trying to cultivate a particular competency in-house (i.e., without the starting point of capability). The merging of two strong, capable companies brings advantages in timeline synergies, information flow, and general project integration without having to sacrifice competency.

Pharmaceutical Technology: What might be a pharmaceutical or biotech company's biggest concerns with using a single-source vendor?

Johnson: I work mostly with small companies, which are sometimes concerned that they won't get the equivalent amount of attention from the contractor as a large pharma company. This is less of an issue when a small pharma/biotech company is working with a small contractor because in that scenario, the client gets to know the executives at the contract organization. When larger CDMOs are created through acquisitions, it is not always possible for clients to get that personal touch from the top.

Also, large companies sometimes have the reputation of being more policy driven than science driven, or of being more bureaucratic and less flexible. Small companies have an affinity toward working with contractors that they perceive to have *modus operandi* similar to their own (e.g., being highly flexible and entrepreneurial). This concern is allayed if a company has a good experience with a large, soup-to-nuts contractor. If the contractor has to make changes on the fly and proves to be responsive and flexible, then the small company will be more willing to sign a contract with them for their next project.

Doug Johnson, PhD
Founder
OCAM Solutions

Pharmaceutical Technology: Do you have any specific examples of how a single-source CDMO may benefit a small start-up company?

Johnson: In one case, a client selected a drug substance manufacturer because of its unique fit between what the vendor had to offer and what the client needed. This was for a Phase I/II clinical supply run. The manufacturer was also able to produce the active pharmaceutical ingredient (API) in capsules, which was exactly what the client needed. A lot of hassle and cost that would have been associated with method transfer was avoided because the methods were very similar. In addition, the timing was more coordinated between the production of the API and the production of the drug product.

In another case, our client did not initially choose to work with a large contractor. However, the vendor they contracted to manufacture their drug substance was subsequently acquired by a larger company. The transition was managed well and didn't create any glitches for the client. They were so pleased with the work done by the drug substance group that they opted to stay with the newly formed single-source company for their drug product work. Even though the client didn't initially plan to use a single vendor, it worked out well.

Pharmaceutical Technology: Are there advantages in terms of when clients begin working with a single-source CDMO (e.g., in Phase III versus early formulation)?

Johnson: There has been a shift on the part of larger contractors to being more interested in working with clients from the beginning. I have two clients for whom this has been particularly beneficial. In one case, the project progressed as far as it could and was put on hold for internal reasons. However, because the same company worked on both sections of their project, it means there will only be one source of data when they have to perform due diligence, which will be cleaner and easier. The other case involved steps in which there were delays. Managing delays in the process is much easier when both the drug substance and the drug product are worked on within the same company because a delay in one company doesn't have to be explained to another. If one company is involved from start to finish, the client's project has the advantage of being less fragmented. ■

A Q&A

Bringing the Single-Vendor Approach to the Pharma Industry

An economist's view of how single-source networks cut development timelines.

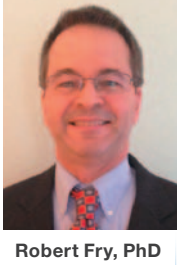
From the perspective of an economist, time is money. And, particularly in the pharmaceutical industry, speed is of the essence. As drug developers face increasing pressure to get their products to market as quickly as possible, the CDMO industry is evolving to meet this need by offering end-to-end services. Here, *Pharmaceutical Technology* speaks with Robert Fry, PhD, who, as a macroeconomist and chief economist at Robert Fry Economics LLC, offers his observations on these important trends. Fry's comments expand upon the conversation started during a panel discussion during CPhI North America 2017.

Pharmaceutical Technology: What are the benefits of a pharmaceutical company (large or small) adopting a single-vendor approach?

Fry: For the pharmaceutical industry, speed is an attractive benefit. I first became aware of the single-supplier production process more than 25 years ago while studying Toyota's lean production system. The single-source network helped Toyota improve its inventory management, but it also enabled Toyota to create faster turnaround times than its competitors. Toyota could launch a new model onto the market every four years when other companies were doing it every five to 10. Toyota was faster, in part, because it was working with fewer vendors; therefore, the car maker spent much less time negotiating contracts and eliminated many logistical problems.

Speed is also an important factor for the pharmaceutical industry. In the context of drug development, where competitors may be developing similar products and where patents expire in a finite number of years, companies want to get their products on the market as soon as possible. Speed is of the essence, which is perhaps the best argument for using a single supplier in the pharmaceutical industry.

Pharmaceutical Technology: During the panel discussion at CPhI North America 2017, you described the single-supplier approach as a middle ground between two ends of a spectrum. Why do you feel that's the case?



Robert Fry, PhD
Chief Economist
Robert Fry
Economics LLC

Fry: The single-supplier model is a middle ground between two extremes. At one extreme, where there are many suppliers in a competitive industry, you have an auction market, where products are bought from the cheapest vendor. In this scenario, the item is a commodity, multiple suppliers are producing it, and many consumers are buying it. At the other extreme is an integrated company that produces the products that it sells.

In some industries, a single supplier is desirable whereas in others, an auction market is sufficient. In the pharmaceutical industry, having a single supplier (i.e., the middle ground) may work better than having multiple suppliers (the auction model) or doing everything in-house (i.e., the integrated approach). Drug development, which is research and labor intensive and involves products that are very specific to the buyer, lends itself to the single-supplier model.

Pharmaceutical Technology: From the perspective of an economist, what is the monetary value of using a single supplier?

Fry: Time is money. Investors require a return on the money they invest. The longer the wait between when the money is expended and when the return on it is realized, the more they require. In the context of drug development, more money is probably spent on good, solid research than on actual materials. In this scenario, what is really being paid for is human capital. In other words, the value of the materials is secondary to the brain power that knows what to do with them.

Pharmaceutical Technology: When a drug maker is evaluating these types of contracts, what are the most critical ingredients?

Fry: When building a contract, expertise is needed from many different areas. It is important to involve an economist or business person. The incentives must be structured such that both parties in a contract are acting in their combined best interest. Good lawyers are required to cover contingencies. It is also important to involve personnel from the technology side. In the context of drug development, it is not a case of simply minimizing the price of materials; the contract should be approached much more holistically.

From an economist's point of view, there should always be a clause in case the cost of a material increases dramatically. For example, if the price of a material doubles, the pharmaceutical client must agree to pay more for it. Otherwise, no one will supply it because it's too risky. Including ways to cover contingencies, such as price index clauses, are important to ensure that risks are shared by both parties. ■

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91% said obtaining greater flexibility in human capital deployment was a key advantage of regulatory outsourcing (1).

Despite growing pains, regulatory outsourcing is a rational response to the increasingly constrained ROI model for drug development. Regulatory outsourcing partnerships can be refined and optimized by following three simple rules.

A partnership should be adaptable to deliver cost-and-operational efficiencies to meet client needs.

Right-size regulatory outsourcing solutions

A company must first define its needs. Does the company require improved efficiency, a re-focusing of responsibilities for key internal regulatory staff, additional expertise, global knowledge, and/or technology implementation?

Once goals are clear, the organization should craft a collaboration that fits its deliverables and costs. Large transformational projects may demand a strategic partnership. Small, transactional projects may focus on compliance and cost savings. For example, a service provider may take over high-volume, high-frequency activities such as document preparation, dossier assembly, and submission publishing.

Relationships can be right sized mid-stream. If a client acquires a portfolio from a third party and must establish affiliate relationships in multiple countries, an existing outsourcing partnership can be modified. A 'virtual' presence can be built in far-flung geographies where it does not make economic sense for the client to maintain a physical presence. A partnership should be adaptable to deliver cost-and-operational efficiencies to meet client needs.

Mind the transition

Regulatory outsourcing, even for small, targeted projects, is a change-management challenge. Staff may worry about the loss of responsibility, or loss of jobs. New processes and systems may be met with resistance. To overcome skepticism and fear, all relevant business units need to understand what the vendor is providing, with transparency for roles and responsibilities.

The vendor can organize and conduct focused workshops designed to ensure that the client's existing regulatory team understands and supports the outsourcing process. A shadowing process to introduce vendor teams to a company's internal teams and to other stakeholders throughout the company can be used. The transfer of work can then be mapped. A rushed transition will likely be a troubled one. Transferring simple, downstream publishing activities to a service provider can take three to six months; a complete transfer of regulatory affairs portfolio management can take up to one year.

Even if existing regulatory information management systems or processes are outdated or inefficient, few companies want to deal with a deluge of changes in addition to adopting an outsourced operating model. Many pharma companies prefer to retain their existing systems but will upgrade to more efficient technology if the benefits are explained and demonstrated rather than dictated.

Support and govern the relationship

Ultimately, a successful outsourcing relationship requires support from top management. In successful large-scale strategic partnerships, appropriate motivation should be given to staff based on compliance and cooperation (quarterly goals, etc.). In this setting, governance and communications between providers and companies work best when function is matched to function, subject matter expert (SME) to SME, therapeutic area to therapeutic area, and local-regional experts to local-regional experts.

A robust governance structure is vital to cultivating and maintaining a healthy outsourcing relationship. In addition to its operational skillset, the regulatory affairs team overseeing a service provider needs to have management expertise.

The relationship's success (or lack thereof) should be measured regularly. Key performance indicators of the outsourcing partner's performance should include staff turnover and efficiency, price predictability, and overall client satisfaction.

An effective outsourcing partner should report both strategic and functional metrics upon demand. Functional metrics should include percentage of on-time submissions, percentage of submissions achieving first time quality, and number of submissions completed versus number planned. Strategic metrics can be measured by a survey targeted to specific stakeholders, which can also elicit new ideas for improving the partnership.

Done right, regulatory outsourcing adds value

Regulatory outsourcing can add new technology, operational expertise, global and local regulatory intelligence, and process innovation to a company's arsenal. Success requires bespoke solutions supported by management and nurtured by robust communication and strong governance.

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New Technologies Optimize API and Drug Product Manufacturing

Amber Lowry

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Innovative new technologies released over the past several months seek to enhance bio/pharmaceutical development and manufacturing.

Over the past several months, manufacturers pushed technological limits to release products to optimize API and drug product manufacturing processes. Some of these technologies include advancements in lyophilization, continuous flow chemistry, process control, and powder handling. Below is an assortment of such products for API and drug product manufacturing.

New systems for lyophilization

Telstar has developed LyoGistics Zero, a vial automatic loading and unloading system for freeze dryers with a contactless magnetic drive for the manufacturing of hazardous products (1). A steam-sterilizable slider uses a passive linear magnetic driving mechanism that functions without racks, belts, or bellows to reduce particle generation and improve cleanliness. The slider remains in the chamber and is cleaned and sterilized with the internals of the freeze dryer. The system is suited for aseptic isolators requiring advanced protection for the operator (Occupational Exposure Limit 5), product (ISO5), and environment.

The Lyometrics system from Telstar provides online monitoring of global batch temperature during developmental or full production conditions in GMP industrial freeze dryers with automatic loading and unloading systems (2). With the use of soft-sensor technology, the system offers a more practical approach to collecting product temperature when production environments are presented with automation and physical obstacles. The software within the freeze dryer control system can non-invasively obtain the average sublimation interface temperature of an entire product batch.

Tools for continuous flow chemistry

Titan, a modular continuous chemical processing system from Syrris, is a turnkey system for prolonged use in demanding manufacturing environments (3). It comprises a range of integrated, rapidly reconfigurable modules, enabling continuous flow processes to be performed on a laboratory scale, or at rates of up to a tonne per day. Reactors are available in 64 and 250-mL volumes and may be connected when larger-scale systems are required. The system offers high chemical resistance, and it can accommodate reaction temperatures from -40 to +250 °C and pressures up to 20 bar at flow rates between 1 and 250 mL/min per channel.

Process control solutions

The Dynatrol CL-10GP Proportional Level Detector controls liquid levels in pilot plants, pharmaceutical processing, and small vessels to obtain proportional level control over an exact range (4). The EC-103C(G) Control Unit is paired with the detector and can activate electro-pneumatic transducers, valve positioners, indicators, controllers, or other direct-current devices. The level detector and control unit monitor and control liquid level range using a high-resolution, proportional output signal. This control operates under varying frequency power supplies or harsh process conditions, such as high pressures and temperatures.

Malema Sensors added SumoFlo, a single-use flowmeter that measures flow rates from 50 gm/min up to 100 kg/min with accuracies within 1% of reading (5). Fabricated from gamma-sterilizable PEEK (polyether ether ketone), the device provides single-use flow measurement solutions for biopharmaceutical manufacturing applications including tangential and depth filtration, buffer dilution, cell cultures and cell harvesting, chromatography, and hygienic fluids with varying density or viscosity. Calibration parameters for each sensor are stored on a radiation-tolerant memory chip allowing the sensors to be interchanged with other SumoFlo electronics transmitter without affecting measurement accuracy.

SupplyCare 3.0 from Endress+Hauser is an update to its Industrial Internet of Things (IIoT) application for tank inventory management (6). The system provides an overview of levels and product inventory in tanks and silos worldwide. Features include hardware and software options allowing level, flow, and pressure data to be displayed at a desk or handheld device, as well as inventory tools. The system uses Connect Sensor FXA30, a battery-powered cellular gateway for remote monitoring of level, flow, and pressure instruments in locations where power is not available. IMS SXS70 Middleware enables the integration of accumulated data with enterprise resource planning or manufacturing execution systems. Hardware developments include Fieldgate FXA42, a gateway that acquires data from local-level flow and pressure instruments and sends it to the local control system, transmitting the data via an integrated web server.

Siemens's Sitrans FS230, a digital ultrasonic flow system, consists of the Sitrans FST030 transmitter and Sitrans FSS200 clamp-on sensors (7). The system includes a digital sensor link that digitizes the signal at the earliest stage of measurement to optimize the signal-to-noise ratio. Because of the system's 100 Hz data update rate and integrated algorithm, the transmitter detects small flow changes for rate accuracy of 0.5 to 1% and zero-point stability. The flow system's patented pipe configuration menu allows the user to select various upstream pipe anomalies and automatically adjusts for flow profile disorders stemming from unfavorable upstream conditions. Other features include comprehensive diagnostics, mounting hardware, built-in startup wizards, and a customizable human-machine interface. Support tools provide direct access to all operational and functional data, certificates, and audit trails. Comprehensive diagnostics facilitate preventative maintenance.

Semi-automatic powder handling technology

The JetBreaker system from ILC Dover is a semi-automatic powder handling system that deaggregates powdered media and buffer powders so that they can be better mixed in solution. Powders such as sodium chloride and ammonium sulfide may require delumping before dispensing into process liquids. According to the company, if the aggregates are not fine enough, they can damage process valves and equipment (8). Tests performed by the company found that the system produced homogenous powder while flowing through a feed hopper into the company's jet venturi mixing systemat 1250 kg/h.

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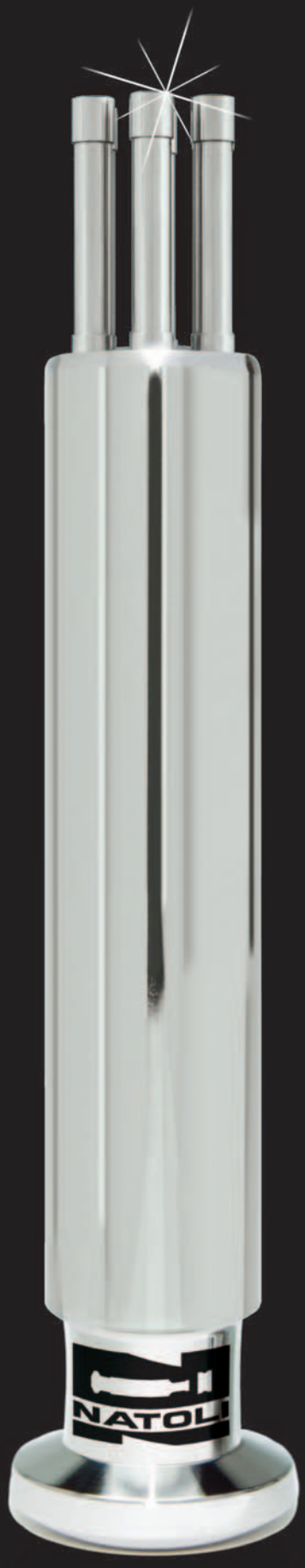

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