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Cover photo: A complete aseptic vial filling line using a unidirectional air flow isolator for the filling process, and a RABS for the capping stage. See article on page 8.

european INDUSTRIAL PHARMACY

Issue 43
February/March 2020

ISSN 1741 4911

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Industrial Pharmacy is published quarterly by:
Euromed Communications
Passfield Business Centre, Passfield,
Liphook, Hampshire
GU30 7SB, UK

Tel: +44 (0)1428 752222
Fax: +44 (0)1428 752223
Email:
publisher@euromedcommunications.com

www.industrialpharmacy.eu
Annual subscription rate £90

Indexed by:
Scopus & Embase

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editorial

Creativity and change

I have always been interested in the creative process and how it comes about. The split between arts and sciences, which happens at a relatively early stage in education, implies that there is a meaningful difference between them. However, many artists and sculptors require detailed scientific and technical knowledge to achieve their aims. The works of Al Wei Wei and Anish Kapur, for example, required exquisite engineering and optical skills. As a scientist, I am interested in how we can bring the creative process into science.

During the mid 1980s I was working as the Head of Solid Dosage Form Development at the Wellcome Foundation Ltd in Dartford, Kent. Wellcome was one of the most creative R&D companies of all time with the discovery of the first antivirals (acyclovir and zidovidine) and the first new anticonvulsant and antimalarials for a generation, amongst many other drugs I worked on.

In Development we were using small scale batch extruders to make pellets by extrusion spheronisation, for coating as extended release dosage forms. I had the idea of using a continuous twin screw extruder in tandem with the spheroniser to produce a continuous process for larger scale use. I set up a trial with Cyril Eardley at Baker Perkins in Stoke on Trent and set about transporting the spheroniser and the materials. The spheroniser weighed about 500 kg and the smallest vehicle with a tail lift of that capacity was a 5-ton truck, so I hired one for a day, drove up to Baker Perkins, and did the trial. The results were mixed; the product quality was largely granular under the test conditions we used but we were able to easily adjust the process to change product quality quickly and easily. The potential for the process was clear.

I published the results of the trial in 1986 and was the first person to publish a paper on twin screw continuous granulation in the pharma industry. When you start a creative process, the output is not always what you expect – but if you don't take the first step, you will never go on the journey!

Michael Gamlen

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TRANSITIONING TO CONTINUOUS PROCESSING FROM BATCH OPERATIONS

by Barry Perlmutter

Batch processing has been the mainstay of production for both pharma and nutraceuticals for the past decades. However, in some production processes like specialty, fine chemical or bulk chemicals continuous production has its advantages. This article discusses the pros and cons of both methods and looks at the preparations required for changing from batch to continuous processing.

Barry A. Perlmutter is an internationally recognized solid-liquid separation expert and is currently President and Managing Director of BHS-Sonthofen Inc. Barry has over 37 years of technical engineering and business marketing experience in the field of solid-liquid separation including filtration & separation, centrifugation and process drying. He has been responsible for introducing many European companies and technologies into the marketplace. His new book, *Handbook of Solid Liquid Filtration*, published by Elsevier, UK in February 2016 is part of a Chemical Engineering series and is referenced by practitioners in the field. He received a BS degree in Chemistry from Albany State (NY) University, MS degree from the School of Engineering at Washington University, St. Louis and an MBA from the University of Illinois.

Introduction

Most chemical operations are batch operated plants. Batch reactors are used where one can control the pressure, temperature, agitation, residence time, crystal seeding and crystal growth. In these batch operations, for filtration, the processes use filter presses, vacuum nutsche filters, filter-dryers, plate and leaf filters and batch centrifuges. Finally, batch dryers are used, such as conical designs, where heating/temperature can be controlled as well as agitation to minimize the effects of the pasty or thixotropic phase on the drying. Batch processing is easy as batch-to-batch integrity and quality can be maintained but significantly lacks flexibility in scaling capacity, and typically requires larger manufacturing footprints and less efficient use of space.

However, batch processing is also making a comeback. For example, most pharmaceutical plants are batch operations so that each batch can be identified for human consumption. Further, as chemical plants become more flexible and toll manufacturers take a larger role in production campaigns, products are changed quickly, sometimes on a daily basis, then a batch process recipe can be implemented much more simply than a continuous process. The same holds true for contract manufacturing organizations (CMOs) or contract development and manufacturing organization (CDMOs), which are organizations which provide comprehensive services from drug development through drug manufacturing.

With the push to become more efficient, many process industries started thinking about continuous processing. For example, a continuous filter is typically ⅓rd of the size of a batch filter. Every engineer is reaching for the "golden ring" to convert to a continuous process to increase yield and optimize quality by

1. using less reslurry/holding/buffer tanks,
2. eliminating transfer pumps,
3. minimizing the complications of solids handling,
4. using less agitation which can impact crystal size and fines generation,
5. maintaining constant flows, pressures and temperatures, etc.

Sometimes it's easy and sometimes it's impossible.

In my career, I have helped engineers move from batch to continuous operations for such applications in pharma and biochemical, specialty polymers, starch and cellulose, aromatic acids and fly ash wetting. Of course, I have also tried and failed with bioprocessing for reaction-filtration and specialty metals processing. But failures are equally as important as successes. Let me give you some examples of successes, which are a lot more fun.

Specialty chemical polymer application

The existing process was a batch crystallizer operating at 0-5 degrees C with 13-20% solids. The filtration was a batch vacuum operation with a 6-inch cake and a heptane wash. Following the wash, there is a drying / blowing step to remove the heptane down to 1.0-0.5% and then the product is fully dissolved in methanol for pumping to another downstream reactor. For an expansion, the decision was to transition to continuous processing to eliminate solids handling and reslurry tanks as well as to reduce the energy costs by eliminating the liquid ring vacuum pump required for vacuum filtration.

After lab and pilot testing, the Rotary Pressure Filter (RPF), shown in **Figure 1**, was selected. It is a continuous pressure filter designed for thin cake (5 mm) filtration,

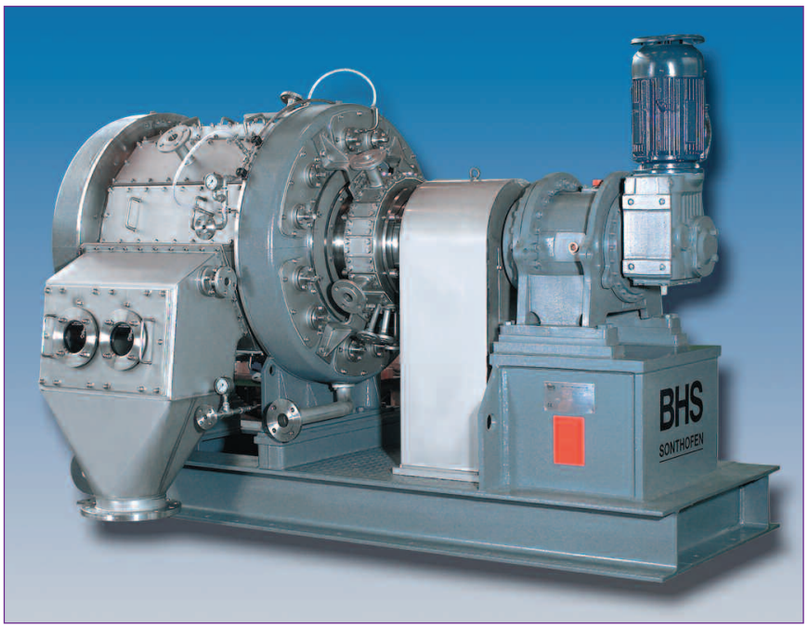


Figure 1 – BHS Rotary Pressure Filter

washing and drying with a slowly rotating drum (6-60 rph). The drum is divided into segments (called cells) each with their own filter media (2-5 um multilayer metal) and outlet for filtrates and gas. The cake from each cell is dissolved with spray bars and directly pumped into the next reactor. Along with the RPF, the client installed a continuous reactor. The RPF startup went very well while the continuous reactor was quite a challenge. This we can discuss at another time.

Protein-lipid biochemical application

This was a new process using animal renderings to produce proteins and lipids. The process was rather involved using formic acid and dimethyl ether (DME) under pressure so that the DME behaved as a liquid rather than a gas. The initial thinking was a batch operation with reslurry tanks; investigations included centrifuges, horizontal plate filters and enclosed filter presses. This phase of the project involved testing for over one year. Unfortunately, while there was a great deal of learnings about the process, the batch operation required many agitated tanks and pumps with a great deal of solids and solvent handling. In addition, these technologies could not maintain the pressure for the DME during cake discharge. The decision was made for continuous processing and again, after special lab and pilot testing, the Rotary Pressure Filter, was selected as shown in **Figure 1**.

The RPF provided the continuous pressure filtration, cake washing and drying/flashing with complete containment. A secondary benefit was a consistent back pressure and cake discharge pressure to keep the DME as a liquid rather than a gas.

Phospholipids pet food additive

In this process the pharmaceutical company extracts phospholipids from egg yolk and prepares the final product as an additive for pet food. In the existing process, the ethanol slurry was mixed in various reslurry tanks for dilution washing and then manual vacuum filtration. For the expansion, it was decided to transition to continuous processing to eliminate the reslurry tanks, improve the cake washing and eliminate the manual handling of solids. As vacuum filtration was a validated process though still a manual operation, the engineers evaluated vacuum belt filters.

The choice was a Continuous-Indexing Vacuum Belt Filter for vacuum filtration, cake washing and dewatering of the cake. The technology is based upon fixed vacuum trays, continuously feeding slurry system and indexing or stepwise movement of the filter media. In practical terms, the operational features of the Belt Filter can be viewed as a series of Buchner funnels.

For the process operation, due to the stepwise operation of the belt, washing and dewatering efficiencies are maximized with the stopped belt and the mechanism of "plug-flow" for gases and liquids. The "plug-flow" or displacement washing efficiency require a lower wash ratio as compared with multiple reslurry washes. Finally, the fixed trays allow for the mother liquor and the wash filtrates to be recovered individually and recirculated/recovered/reused for a more efficient operation. The client installed the fully enclosed and pressure-tight unit of 2.25 m^2 of filter area for the egg yolk powder and ethanol slurry, as shown in **Figure 2**. The filter is validated, as a GMP installation, for pharmaceutical production and has increased the yield of the phospholipids by 3-5 %.

Initial batch process for lab/pilot plant to continuous process for demonstration/ production process

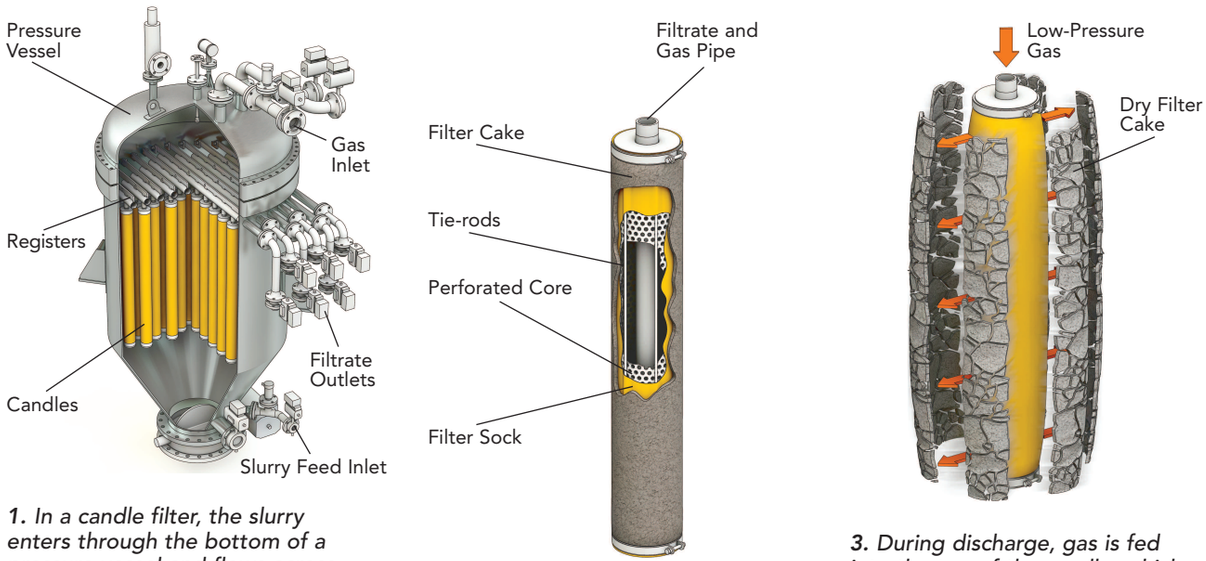
This was another interesting case study which illustrates how the process can be changed based upon the scale of operation. The researchers, during their development, used batch reactors followed by batch filtration, cake washing and drying. The liquid, succinic acid, is the product from a natural feedstock while the cake is waste. In the lab/pilot scale, batch candle filters were used, as shown in **Figure 3**. However, as the process development continued, there were additional washing steps with different liquids. During the transition stage from lab researchers

Figure 2 – Contained Continuous-Indexing Vacuum Belt Filter

to process and project engineers, it became apparent that batch candle filters would not be able to handle the multiple operations. Further testing on a larger scale resulted in a more reliable continuous process with vacuum belt filters, as shown in **Figure 4**. The lessons learned for process engineers, from this example, is that the process scale has to be taken into account and that what works in the lab may not work in the plant.

Continuous and batch operations in the same process line

In this bulk pharma/specialty chemical application, each step of the process required a different continuous or batch operation. The engineers approached the project from a "continuum" or "holistic" view and looked at each step individually and then in total. The two reactors were batch operated. They feed one continuous-indexing vacuum belt filter (see **Figure 2**). From the continuous belt filter, the solids are discharged in a



***1.** In a candle filter, the slurry enters through the bottom of a pressure vessel and flows across the filter media. The filter candles are attached to registeres that collect hte filtrate. Gas is fed into the top of the pressure vesel for cake drying discharge.*

***2.** During operation, filtrate exits from the top of the candle, while the solids collect on the synthetic filter sock.*

***3.** During discharge, gas is fed into the top of the candle, which expands the flexible filter sock. This causes the dry cake to crack and break away from the filter. The solids are collect at the bottom of the pressure vessel.*

Figure 3 – Batch Candle Filter Operation

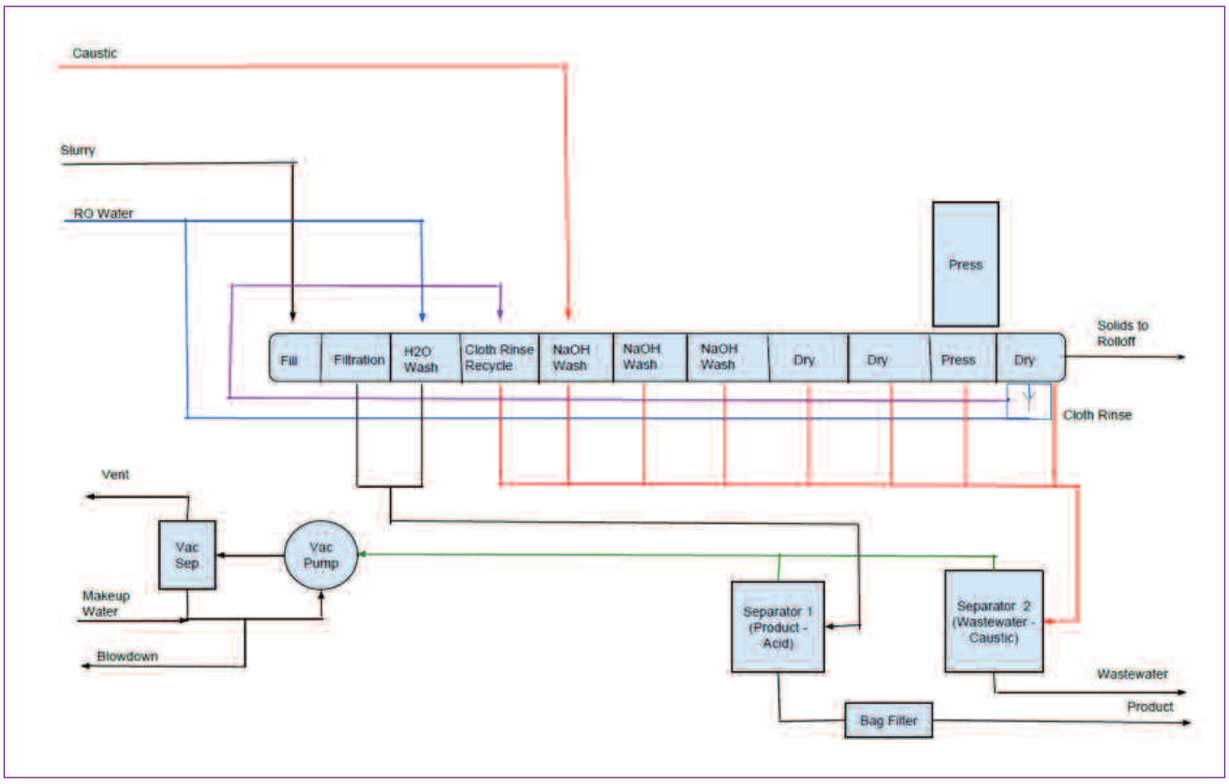


Figure 4 – Commercial Scale Production Operation

concentrated wet cake and fed to a fully-contained batch filter press. The dried cake from the batch filter press is packaged for final processing at another API (active pharmaceutical ingredient) plant. As in the previous example, process engineers need both a "silo" approach to the optimization as well as a "continuum" approach to understand how one upstream decision may impact the down-stream process.

Final thoughts

The current state of batch versus continuous processing depends upon the process, product and type of application. For specialty or fine chemical operations, continuous processing is becoming more prevalent. For pharma and nutraceuticals, batch remains the choice. For bulk chemicals, continuous processing is generally preferred. However, with this in mind, there are no rules and if a process can be transitioned from batch to continuous, the benefits will be clear.

Preparing to make a transition from batch to continuous processing operations requires more than just new equipment: it demands a transformation of the entire manufacturing operation and the mindset of the staff. Operators accustomed to batch processes will need to be retrained, not only on individual pieces of equipment but also on the new, broader manufacturing strategy. The choice of the "continuous" vendor is also critical to support the transition.

Process engineers have many choices to transition to a continuous operation. Testing, both lab scale and pilot, is necessary to support the decision. A continuous operation is more challenging, as being a "steady-state operation" there are less chances to make a change so automation/ instrumentation and controls must also be updated; or as the new thought is "digitalization" of processes and plants. In the end, whatever you decide, you need to be ready to face new issues during commissioning and start-up. I can tell you, first-hand, there will be many unexpected consequences.

You can follow my blog at my https://perlmutter-ideadevelopment.com/ and my "Handbook of Solid-Liquid Filtration" at https://www.elsevier.com/books/solid-liquid-filtration/perlmutter/978-0-12-803053-0 for further insights.

STANDARDS FOR PHARMACEUTICAL ISOLATORS: AN OVERVIEW

by Tim Coles

Pharmaceutical isolators have wide application in critical processes such as aseptic filling and genetic engineering, and yet they are not covered by any specific UK, or international standard. At present, users have to rely on standards essentially written around cleanrooms, which are a very different contamination control system. There is also one standard which is a sub-section of an aseptic processing standard. This paper highlights areas where these existing standards are perhaps deficient.

Tim Coles, BSc (Hons), M.Phil., Technical Director, Pharminox Isolation Ltd., has worked in the field of isolator technology for over twenty years. He was a founding member of the UK Pharmaceutical Isolator Working Party that produced *Pharmaceutical Isolators*, Pharmaceutical Press, 2004, and more recently of the PDA committee that produced Technical Report No 51. "Biological Indicators for Gas and Vapour Phase Decontamination Processes" [for the validation of isolator sanitisation]. His book *Isolation Technology – a Practical Guide*, CRC Press Inc. 2004, is now in its second edition.

Existing isolator standards and guidelines

When gloveboxes first came into general use in the pharmaceutical industry, around 40 years ago, there were no specific standards available to give guidance on their design, construction and operation. Today, decades on, there is still no standard directly relating to what we now term 'isolators'. Instead, we rely on a mixture of cleanroom standards such as the ISO 14644 series of standards[1-6] and containment standards such ISO 10648.[7-8] Perhaps the most focussed current document is ISO 13408-6; 2005.[9] At the time of writing this standard is under periodic review at the DIS (Draft International Standard) stage – ISO DIS 13408-6.[10] It is also just one part of a standard devoted to aseptic processing, thus leaving aside the all-important containment aspect of isolator technology. There are also guidelines such as the book *Pharmaceutical Isolators*[11] and, of course, *EU GMP Annex 1*.[12]

Where aseptic applications are concerned, ISO 14644 is useful and informative, but it has a fundamental flaw in relation to isolators: cleanrooms are manned by human operators. As a result, the greater part of these standards are devoted to the means to first minimise, and then to manage, the particulates generated by personnel. Isolators, by definition, do not have to accommodate human operators and, as a consequence, are liberated to be designed, constructed and operated in completely different ways.

One very significant advantage of isolators over cleanrooms, in aseptic operation, is the capacity for gas-phase or aerosol bio-decontamination. Hydrogen peroxide has become the biocidal agent of choice for sound reasons but, here again, there are no definitive standards. However, ISO DIS 13408-6 does provide considerable discussion, and the PHSS Guidance Note No. 1[13] gives a lot of practical guidance following MHRA comment on the application of vapour phase hydrogen peroxide in isolator bio-decontamination.

Where toxic or pathogenic applications are considered, ISO 10648 is again useful and informative, but essentially comes out of radiological protection, and is very dated. Significant advances have been made in containment isolators over the last 25 years and therefore design, construction, testing and operation standards are surely due for review.

Where the application is both aseptic and toxic, as for example in the preparation of cytotoxic parenteral solutions, the ISO standards 14644 and 10648 are of limited use since neither cover this situation, and ISO DIS 13408-6 is technically not applicable.

It is clear that both aseptic and containment isolators offer major advances over previous technology, but neither is covered by specific standards. The UK Pharmaceutical Isolator Group (UKPIG) did start down this route, but the organisation effectively closed down in 2005 when the driving force, Brian Midcalf,[i] retired. Standards in general, and ISO standards in particular, take a long time to develop and be published, often years and sometimes decades, as in the case of EU GMP Annex 1. It seems unlikely that any individual or group is likely to take up the official challenge in the near future, but perhaps some unofficial draft standards could be drafted in the meantime.

What aspects of isolator technology might such drafts tackle, where the current standards fall short? One is the apparent anomaly in airborne particulate figures, where EU GMP Grades A and B do not seem appropriate for isolators. Although the industry should be adopting ISO standards for airborne particulates, many operators still prefer to use the EU GMP designations. Both Grade A and Grade B permit up to 3,520 particles of ≥0.5µm per m^3. In terms of isolator

i Brian Midcalf very sadly died in 2019.

technology, such a particle burden is appalling! Even a turbulent flow isolator will give virtually zero particle count at rest. If an isolator gives ≥0.5 µm particle counts above a few tens, there is likely to be an investigation. Why then do we apply cleanroom standards to isolators? The regulators in general, and the MHRA in particular, are keen to advance the technology of pharmaceutical production where possible. This being the case, the particulate standards for isolators need to be addressed to match the achievable results.

The threshold limits for airborne particles in isolators might perhaps look something like the values shown in **Table 1**. These are all very much lower than the 3,520 particles allowed under both A and B grades of EU GMP Annex 1.

Some guidance would be needed as to how and where particle counting is to take place in the isolator.

Total particle counts of course include the all-important sub-set which are the viable particles. Here again, the much better environmental conditions inside isolators offer the possibility of setting more stringent standards, however it may not be possible to set better values than those tabulated in the EU GMP for purely practical reasons. *Pharmaceutical Isolators* offers a set of viable particle limits for isolators and states "This represents a reduced acceptance level for settle plates compared to the EC [sic] GMP guidance." This probably represents the current best standard for viable particles in isolators.

Moving on, it would seem reasonable to set some standards for the basic functional aspects of isolators. It is primarily the flow of HEPA filtered air through isolators which provides the clean conditions. In unidirectional airflow (UDAF) isolators, which are normally down flow, the requirement is easily defined as the conventional 0.45 m/s, plus or minus 20%. However, an isolator standard might present a requirement to demonstrate unidirectional airflow down to a specific height above the work surface. A suggested minimum make-up air flow rate might also be proposed, for example 10% of the unidirectional airflow. In the case of turbulent flow isolators, an isolator standard should set a minimum air change rate of perhaps 60 total air changes per hour. It could go on to require demonstration that the turbulent flow purges all parts of the isolator volume, and that there are no standing vortices which would retain airborne particles for long periods of time. Further demonstration might include a maximum purge-down time from, for example, GMP Grade D particle burden, down to the values given in the conjectural table above.

Figure 1 – A complete aseptic vial filling line using a unidirectional air flow isolator for the filling process, and a RABS for the capping stage

HEPA filtration of the air passing through an isolator is, of course, fundamental to operation, both for positive and negative pressure applications. Cleanroom standards do offer some guidance, but an isolator standard could be more specific. The need to fully test the supply filters on aseptic isolators, and the exhaust filters on containment isolators, is paramount. Our conjectural standard might specify correctly-sited and well-labelled DOP test ports, and it should place defined limits on the measured filter penetration, under test. Again, some discussion would be needed to set these values, involving filter manufacturers and isolator users. This issue really has to be addressed with absolute clarity in any isolator standard.

Isolator operating pressure is generally viewed as a primary aspect of isolator function, although studies in the past have indicated that isolator pressure is actually not a critical parameter in achieving the required conditions. *Handling cytotoxic drugs in isolators in NHS pharmacies*[14] states: "As stated previously, there is much more to consider than merely the pressure differential of the system. If the above sources of exposure and

Table 1: Suggested maximum number of particles ≥0.5 µm per m^3 for isolators

	Unidirectional flow isolator	Turbulent flow isolator
At rest	5	50
In normal operation	50	500

product contamination[ii] can be minimised, then the type of system selected should be less important. This assumes that there is no catastrophic leakage. In this case, alarm systems and training systems become paramount." That said, an isolator standard might reasonably require that the isolator holds a sufficient pressure so that a positive pressure isolator cannot go negative during rapid glove withdrawal, and a negative pressure isolator cannot go positive during a rapid glove insertion. The standard might also promulgate a maximum time for return to set pressure after a given fluctuation. Beyond this, the standard might offer an acceptable range of pressures for positive pressure aseptic work, and for negative pressure toxic containment.

Leak rate is an issue which exercises isolator users considerably, and here the standards ISO 14644 Part 7 and ISO 10648 Part 2 do actually provide us with a choice of four classes of leak rate with which an isolator might conform. However, there is no guidance as to what class of leak rate is appropriate to what application and manufacturers still use leak rates other than those specified in these standards. Furthermore, there is very little guidance as to how the leak rate should actually be measured in practice: what test pressure should be applied, what should the length of time be for the test, what decay value is appropriate, and should changes in atmospheric pressure and isolator temperature be considered. A standard might offer a range of suitable tests, and the limits which would be applied.

Table 2 shows a suggested structure for isolator leak rate and application.

In passing, EN 12298:1998[15] mentions the concept of BATNEEC (best available technology not entailing excessive cost) with regard to leak rates, but offers no further

ii The factors specific to product contamination are listed in the preceding section of the document.

Figure 2 – A flexible film half-suit isolator designed for sterility testing, using roof-mounted HEPA filters for turbulent air flow, and fitted with an on-board hydrogen peroxide vapour generator for bio-decontamination. This isolator also incorporates instrumentation of the hydrogen peroxide concentration at both high and low levels.

Table 2: Suggested isolator leak rates by application

ISO Class of Leak Rate	% Volume Loss per Hour	Application
1	0.05	Class 3 MSCs
2	0.25	Negative pressure aseptic isolators. High containment isolators.
3	1.00	Positive pressure aseptic isolators. Medium containment isolators.
4	10.0	Not applicable

Figure 3 – A flexible film half-suit isolator for sterility testing, specially-designed for use in a room with a low ceiling, the HEPA filters therefore being mounted on the walls of the canopy. The control system maintains a set canopy pressure via two-fan ventilation, and provides digital display and alarms on the air flow rate and the canopy pressure.

guidance. ISO DIS 13408-6 ducks the issue of leak rate and refers the reader to ISO 14644-7, which means yet again, the user has to sort through another document to find the appropriate information.

Some consideration might be given in an isolator standard to the issue of instrumentation and alarms. This is a topic which is singularly lacking in the otherwise quite comprehensive ISO DIS 13408-6. A relatively small isolator once reviewed by the author boasted over 400 separate alarms, of which the manufacturer declared over 80 as critical. Only five factors are critical to the general operation of an isolator:

1. HEPA filtered air-flow rate, either UDAF or turbulent. This is easily measured and alarmed.
2. Isolator pressure. Whilst isolator pressure does not seem to be critical as such, it is a strong indicator that the isolator is working as normal. For this reason, it should be standard practice to fit an alarm system on the isolator pressure gauge. Such an alarm might be arranged to operate on both high and low excursions from the values set by either the isolator manufacturer or the user.
3. Pressure drop across the main filter is often measured and alarmed.
4. HEPA filter integrity. This can only be measured during DOP testing and is not 'alarmable'.
5. Leak rate. This can only be measured by out-of-service methods and is also not 'alarmable'.

Thus, the only critical alarms on an isolator are, in practice, the air-flow rate, the pressure inside the isolator and the pressure drop across the main filter. Any standard should note this. Failures, other than HEPA filter integrity and leak rate, will show up as changes in these three parameters and therefore do not need to be alarmed as such. That said, it is comforting to have an indication of what item has failed, when an alarm does occur. For example, if the pressure in a pneumatic door seal were to drop below a set value, a message to this effect would allow rapid remedial action.

Various existing standards give an indication of the requirements for the bio-decontamination of aseptic isolators (e.g. BS EN 14937: 2001[16]), but again none are specific. ISO DIS 13408-6 alone provides quite good discussion of bio-decontamination, and is recommended as a useful guide. The application of hydrogen peroxide to the bio-decontamination of isolators perhaps merits a whole standard in its own right, however an isolator-specific standard might give some basic requirements for bio-decontamination. This could, for instance, list the demonstration of log 6 reduction of *G. stearothermophilus* spores, and aeration down to 1 ppm before opening the isolator, as primary bio-decontamination requirements.

Isolator room conditions would really have to be addressed by the proposed standard. In theory of course, room standards need not be high since the isolator, by definition, provides the required standard for the process. In reality, defined isolator room conditions are needed for setting up the open isolator, for cleaning, and for minimising the bio-burden on the isolator and its transfer systems. Leading on from this, a standard might indicate the minimum requirement for garments and gowning for given isolator applications and the room conditions.

On a personal and more general point, standards such as ISOs can be difficult to read and to interpret in a practical sense, even when numbers and values are provided. To some extent, this may stem from the fact that they are drafted by committees, often with varied cultural backgrounds and languages. This is apparent in ISO DIS 13408-6 which whilst containing much useful information, is illogically organised, and needlessly repetitive in places. Final editing by a native English speaker might be helpful in this respect.

Conclusions

Clearly, a standard for pharmaceutical isolators could be extended into a lengthy document including the many aspects of isolator design, construction and operation. As mentioned, the application of hydrogen peroxide vapour to bio-decontamination, could in itself be the subject of a standard. However, a practical and workable standard needs to be pared down to the basics for safe operation. It needs to lay down absolute requirements, but it also needs to offer a range of values or choices where appropriate. Both isolator manufacturers and isolator users are naturally keen to conform to standards, but standards tend to flag up various parameters, without providing applicable values or numbers. Clearly standards cannot be highly prescriptive, but the audience for isolator standards is quite desperate to see figures they can use in practice. Perhaps a set of guidelines in the format of a standard might be established in the first instance.

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This article first appeared in *Clean Air and Containment Review*, Issue 40, 2019.

OPPORTUNITIES AND APPLICATIONS OF 3D DRUG PRINTING IN PHARMACIES

by Josep M Guiu[1,2], Netta Beer[3], and Robert Moss[1,4]

3D printing of medicines is a novel technique that promises a more personalized and patient-centered approach to the manufacture of medicines. In this article, based on a talk given at last year's FIP World Congress in Abu Dhabi, the authors look at the pros and cons of such a radical shift in technology as applied to future human health care.

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Introduction

3D printing is a disruptive technology that has the potential to cause a paradigm shift in the way that drugs are designed, produced, and used. 3D printing is an additive manufacturing technique that enables the fabrication of computer designed objects in a layered manner. 3D printing has been used in many different fields for different applications. In medicine it has been used especially in dentistry and orthopaedics, for the production of prosthetics and implants, and also for producing stents, including drug–eluting stents and implants.

Pharmaceutical applications

More recently, 3D printing research has exponentially grown in the pharmaceutical field, driven by the Food and Drug Administration (FDA) authorization of Spritam® (levetiracetam, a drug used to treat epilepsy) in 2015[1]. One of the advantages of Spritam® over previous levetiracetam versions is highly porous layers that increase its dissolvability due to the fact that the powder-bed 3D printing technique boasts porous layers. Although this was a landmark case with the introduction of 3D printed drugs in therapy, it is a case of the pharmaceutical industry using 3D printers for the mass production of registered drugs. Thus, this case had no real influence on the possibility of printing 3D medicine in pharmacies, but it did spark the interest and imagination of researchers and pharmacists to see how 3D printing might be applied in the pharmacy setting.

There are different definitions and interpretations of what personalised medicine means. While some limit this term to medicine adapted to groups of people with a certain genetic property, others take a more individualized approach and believe that medicine should be personalized on an individual basis according to the specific patient's characteristics, including age, weight, metabolism, co-morbidities, medication history and lab results. While some believe personalized medicine will eventually change the current drug development and manufacturing practices, others are sceptical about this prediction and believe that it will always be limited to very specific groups of patients and/or medicines. Either way, production of highly personalized medicine for individual patients is already a reality in pharmacies today.

Traditional drug compounding

Compounding or production of magisterial preparations has always been one of the integral roles of pharmacies. Compounding practices and regulations differ between countries and are intended for cases in which registered products are not suitable for the patients. These individualized medicines are often required for paediatric patients but are also relevant for elderly patients or patients with metabolic impairments. Traditional drug compounding comprises sequential manipulations to build a homogeneous mixture of powders, suspensions, or solutions from various amounts of starting materials. This process is both time consuming and labour intensive. It requires training and knowhow of pharmacy staff, as well as adherence to GMP-like standards for the staff, production processes and location of the compounding. Solid preparations include capsules more often than tablets. The production process is often carried out with traditional equipment that relies on the pharmacist's skilled hands and is difficult to complete with accuracy.

3D printing drug compounding

With 3D printing arise opportunities to design and produce medications in an automated manner, which can save on resources and achieve safer and more precise compounded formulations. The different 3D printing techniques would be capable of coping with compounding challenges arising from highly precise dosing, coating of surfaces, production of slow-release galenic forms, formulation of gastric acid-resistant coating, complex release kinetics formulations, and easily dissolving hydrogels for dysphagia patients or

for elderly patients who have difficulties with swallowing. In addition to the ability of creating polypills by combining different APIs in the same tablet, 3D printing also enables the production of medicines taking into account the patient's individual preferences such as shapes, size, colours and flavours (see **Figure 1**). These new attributes could improve patient's adherence to their medical treatments[2,3]. An additional advantage is, arguably, that the new technology might minimize waste production[4]. The automation of the technology could also provide further protection for pharmacists and technicians from exposure to hazardous ingredients, which is becoming increasingly important in healthcare institutions. Another important advantage of 3D printing on-site is when time is a critical factor, for example, when compounding and delivering low-stability drugs.

Although there are many possible advantages to 3D printing as a compounding technology, there are several factors which need to be taken into account with its introduction in the daily routine of drug compounding in the clinical setting[5]. The main barriers relate to the technical aspects as well as the societal aspects of implementation[6]. Technical challenges include the fact that printers, software and materials are still being developed and, for the moment, compared with current compounding techniques, the printing techniques are still slower and not as safe as traditional compounding methods. The societal aspects include legal/regulatory and organizational challenges. These will need to be overcome before adoption of this technology is possible. An important organizational issue is the need to replace existing equipment with the new 3D printers. This represents not only an important investment for the organization, but a major effort in upgrading professionals with a new technology that is continuously evolving with currently few potential products to be compounded. The adoption of the 3D printing technology might also necessitate acquiring new compounding competences for clinical pharmacists, and possibly introducing the challenge of integrating biomedical engineers into a multidisciplinary pharmacy team in more complex pharmacy environments.

Regulatory aspects

As for the legal and regulatory side, the main challenge is that there is currently no regulatory framework or guidance for 3D printers and 3D printed drug products. When producing large batches, quality control relies on the testing of the final products, while in the compounding situation where only a small amount of the same medicine is produced, it is often not possible to check the final product. In these cases, the quality of the product relies on in-process controls, and it is still unclear which in-process controls can be applied to 3D printing. Moreover, in the hospital or community pharmacy setting, 3D printing would most likely depend on the pharmaceutical companies to provide the intermediate products for the on-site printing, which also need further regulation.

Figure 1 – Examples of mock 3D printed tablets. Photo courtesy of Mark Fastø

Conclusions

At the moment, just pilot studies in the clinical trial setting[7] have been conducted in the hospital pharmacy setting, where 3D printing offers a feasible, rapid and automated approach to prepare oral tailored-dose therapies in a hospital setting. These first experiences are the beginning of a learning curve to overcome difficulties concerning the adoption of this technology.

Nonetheless, once the technical, organizational and regulatory hurdles are overcome, implementation into practice of 3D printing could be attained, changing the face of pharmaceutical manufacture and initiating a new era of digital production in pharmacy practice. In this scenario, we can envision that point of care pharmacy-based drug production may be the future of pharmaceuticals.

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THE FUTURE IS NOW! THE EVOLUTION OF PHARMACEUTICAL EDUCATION

by Stefan Grgić

Stefan Grgić , Mpharm, is EPSA Educational Affairs Coordinator 2019/2020. After obtaining his MPharm Degree, Stefan has been working as Research Assistant at the Research Institute for Health and Medical Sciences in Dubai. In April 2019, he joined EPSA as the Educational Affairs Coordinator, and in November 2019 joined the DIA (Drug Information Association) as Junior Scientist. Believing that academic studies familiarize students with only a few aspects of Pharmacy, Stefan emphasizes that soon-to-be pharmacists are not prepared or taught to face obstacles and challenges in the current job market. Therefore, Stefan's activities in EPSA are oriented towards overcoming those challenges while giving the opportunities to students to acquire a lifelong learning mindset through projects like Educational Chronicles, Methodology Booklet and LifeLong Learning Platform.

One of the main pillars of the European Pharmaceutical Students' Association (EPSA) has been and will always be – *Education*. For this reason, EPSA has always been a pioneer in showcasing the most contemporary and significant matters in the world of pharmacy to the European pharmaceutical youth.

Historically speaking, pharmacy, as a discipline which combines science and art, has been evolving, changing and adapting with the needs of the global population.

Today, the word pharmacy means so much more! Community pharmacy, clinical pharmacy, ambulatory pharmacy, compounding pharmacy, industrial pharmacy, regulatory pharmacy, etc. There are countless adjectives which pair perfectly with the word pharmacy, and we gain countless possibilities to perceive pharmacy in that particular aspect. This is why pharmacy, as a sophisticated synergy of life sciences, health sciences as well as social sciences, is simply and in one word - unique.

To help pharmaceutical students of today become highly competent pharmacists of tomorrow, EPSA released its first Methodology Booklet in October 2018. This is a document based on the opinions of 1478 European pharmaceutical students and recent graduates on the teaching methodologies currently utilised by the European faculties of pharmacy. This advocacy tool assists educators and policymakers to continue to evolve and improve European pharmaceutical education. Since education is developed continuously, this will help us to showcase what students and recent graduates think of the current situation of the methodologies applied to teaching and what they want for the future regarding education. Higher education should facilitate the gaining of the knowledge we all aspire to. We believe that continuous dialogue is important and we endeavour to motivate students and recent graduates to seek further

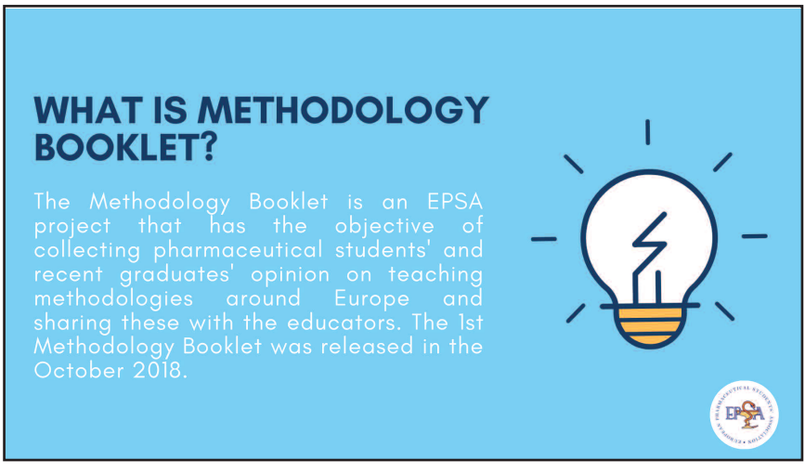

Figure 1 – Methodology Booklet.

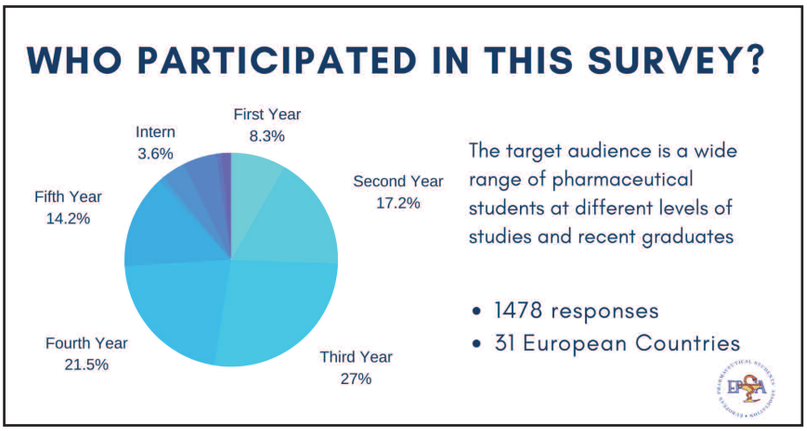

Figure 2 – Survey participants

knowledge and opportunities. Our cause is supported by the European Association of Faculties of Pharmacy, and together we evaluate the process of teaching and learning, and tailor it towards the expected knowledge and competency development among the European pharmaceutical youth.

In order to ensure a continuous promotion and preserve a strong voice within Europe, for the next five years EPSA will focus on four Annexes which will go hand in hand with the Methodology Booklet and represent a more detailed follow up on the main outcomes of the Methodology Booklet itself:

- 1st Methodology Booklet Annexe 1: Soft Skills
- 1st Methodology Booklet Annexe 2: Teaching Methodologies Techniques
- 1st Methodology Booklet Annexe 3: Unification of Curricula in Europe
- 1st Methodology Booklet Annexe 4: Mandatory Internships

As much as it is important to advocate for a better acquisition of knowledge, and familiarising pharmaceutical students with the versatile aspects of the world of pharmacy, it is of equal importance to focus on the transition from student to an emerging professional.

This is something EPSA recognised and in November 2019 launched a new project - Educational Chronicles, which take pharmaceutical students on the lifelong journey of learning and continuous professional development. It also helps them to learn more about the necessary education for a soon-to-be pharmacist to pursue a meaningful career. Educational Chronicles is conceptualised as a set of online

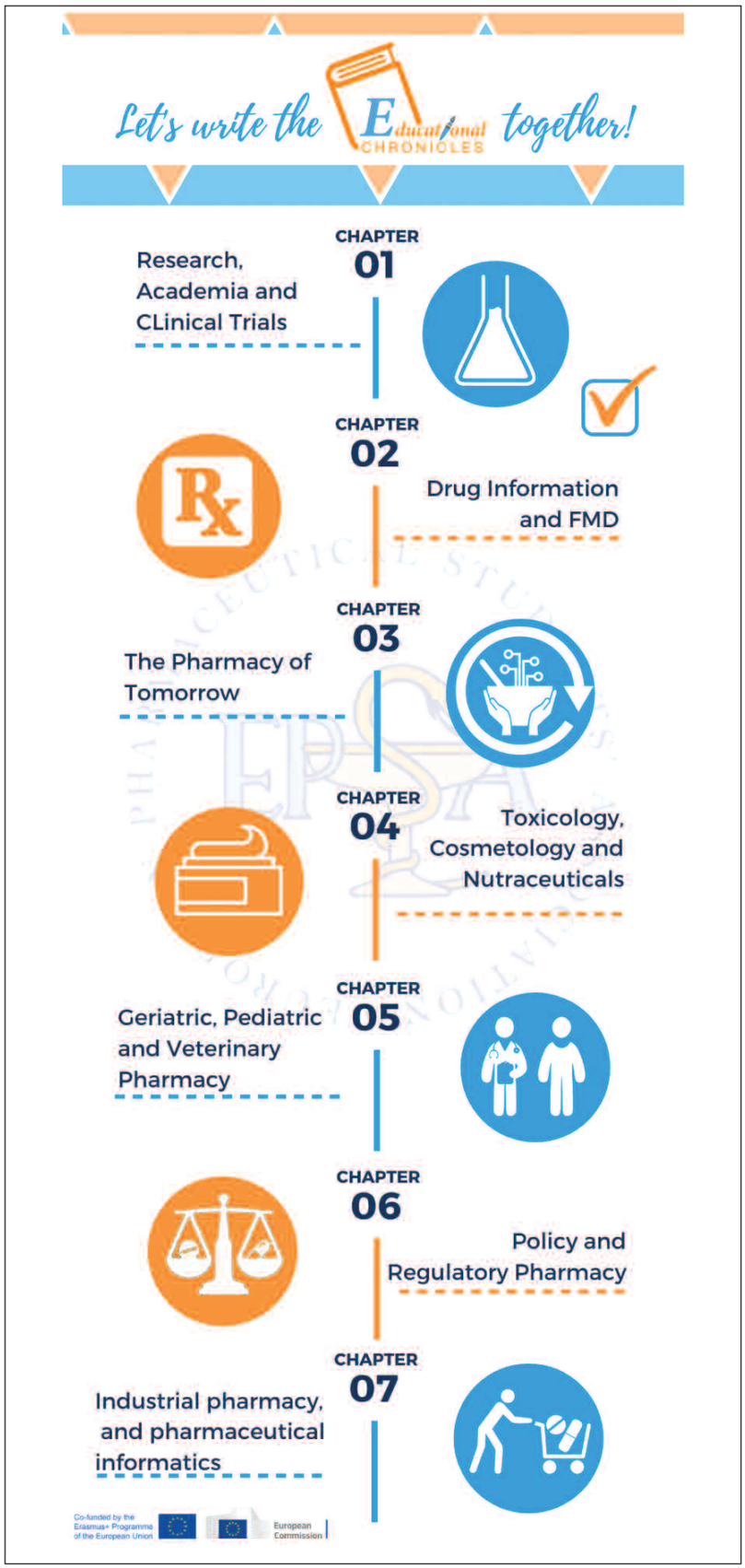

Figure 3 – Educational Chronicles

activities consisting of seven Webinars, called Chapters. Three Chapters have been organised on the following topics:

- Educational Chronicles Chapter 1 - Academia, Research and Clinical Trials in collaboration with EUFEPS (European Federation for the Pharmaceutical Sciences) and ACRP (Association of Clinical Research Professionals)
- Educational Chronicles Chapter 2 - Drug Information in collaboration with EAHP (European Association of Hospital Pharmacists)
- Educational Chronicles Chapter 3 - The Pharmacy of Tomorrow in collaboration with PGEU (Pharmaceutical Group of European Union) and ESCP (European Society of Clinical Pharmacists)

The remaining four chapters will be organised this year (2020), with a special focus on the educational background necessary in Regulatory and Policy Affairs in Pharmacy, along with Quality Control and Quality Assurance, while emphasizing the importance the aforementioned fields have in the pharmaceutical industry. Furthermore, pharmaceutical students will have the opportunity to learn more about Regulatory CMC, Market Access and Marketing Authorization – which are essential aspects within the pharmaceutical industry, yet very obscure to students. Pharmaceutical students, and students with a life science background in general, who are highly motivated towards starting their career in the pharmaceutical industry remain unaware of both the opportunities and the variety of possibilities pharmaceutical industry has to offer. EPSA would like to provide students with a glimpse of this whole other world, yet very important aspect of pharmacy in general.

With the immense expansion of knowledge, scientific and technological achievements, along with the pharmaceutical industry, pharmacy continues to be described as a discipline of lifelong learning.

As pharmacists of tomorrow, both students and graduates need to be updated with the current and ongoing trends within pharmacy and the pharmaceutical sciences. Therefore: *"Tomorrow's illiterate will not be the man who can't read; he will be the man who has not learned how to learn."*

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PHARMA IN PLENARY

EU Pharma in the Aftermath of Brexit

by Nicola Davies

Brexit became a reality on 31st January 2020, when the UK left the EU. For the next 11 months, the UK will remain in a transitionary period where it will still follow EU rules.[1] However, what does Brexit mean for the EU pharmaceutical industry?

The imminent problem now is the possibility of a 'no-deal' Brexit once the transition period is over, which would mean a complete dissolution of all of the UK's ties to the EU. A no-deal Brexit would effectively disintegrate the complex medicine markets of Europe.[2] It is noteworthy, however, that analysts have suggested that a 'soft' Brexit - withdrawal from the EU while maintaining some ties - could still happen as an alternative to a no-deal.[3]

Many Challenges Ahead

The UK being part of the EU meant the ability to participate in a single market that allowed goods and money to be freely transacted over borders. After Brexit, disentangling the political and economic ties that came from decades of participation in this market is likely to be a long, difficult, and messy task.

While Brexit has created some level of uncertainty for most sectors, this uncertainty could be detrimental for the pharmaceutical industry in particular. Take product development, for instance; drug development takes years and needs to be planned in advance. Drug supplies also need to be planned out and monitored. Market approval and shipping of drugs are other areas that Brexit is expected to impact.[4]

Post-Brexit Medicine Shortages

The Brexit Health Alliance reports that approximately 45 million packs of medicine go from the UK to the EU annually.[5] Post-Brexit hurdles in moving goods across borders could result in temporary, but crucial, medicine shortages for both the UK and EU countries.

The same report suggests that since half of the assessment work needed for the authorization of new medical devices takes place in the UK, it is likely that patients in the EU may face delays in being able to use new medical devices. It is also likely that certain standard medical devices may not be available to patients. For instance, large volumes of the needles and tubes needed for blood collection were supplied from South West England to the rest of Europe before Brexit.[6]

The European Federation of Pharmaceutical Industries and Associations (EFPIA) has called for measures such as allowing the use of fast track lanes or priority routes for medicines at airports when it comes to shipping, as well as the necessary paperwork being completed away from the border to save time. Additionally, the EFPIA suggests that active pharmaceutical ingredients or medical raw material be declared exempt from border checks.[7]

The European Medicines Agency (EMA) has a dedicated task force attempting to deal with potential drug shortages by minimizing supply disruptions and developing strategies to manage disruptions that are *already* present in the supply chain.[8]

It is important to note, however, that such medicine shortages can be reasonably expected but are not confirmed yet.[9] Confirmed shortages are promptly reported by the EMA and similar medical authorities.[10]

Changes in Regulations

The UK played a significant role in drug regulation in the EU pre-Brexit through the Medicines and Healthcare Products Regulatory Agency (MHRA). Before Brexit, it contributed up to a third of the EU's pharmacovigilance work.[11] The MHRA will need to be replaced post-Brexit, and finding similar expertise in that capacity is a challenge that could affect drug regulations.[12]

The EMA's relocation, discussed next, also impacts drug regulations. Indeed, uncertainty surrounding Brexit is especially relevant when it comes to medical regulations, with many questions regarding pharmacovigilance activities remaining unanswered. This is where regulatory professionals in pharma need to take the lead and mitigate risk. The Regulatory Affairs Professionals Society (RAPS) is among those keeping an eye on such issues during this shaky transition period.[13]

The EMA's Relocation

The key EU medicines regulator, the EMA, has been required to close its pre-Brexit London office of 24 years and to relocate to Amsterdam. The closing of the EMA office has resulted in around 900 people losing their jobs because they did not wish to leave London.[14]

Although a certain amount of staff losses can be absorbed under its post-Brexit business continuity plan, the EMA could still lose more staff. The worst-case scenario in this situation is that the EMA might not be able to protect the health of EU citizens, as is its mandate. There could even be permanent damage to the country's medicine regulatory system.[15] If forced to invoke its

business continuity plan, the EMA will have to decrease its activities to limit the impact of Brexit uncertainty on public health.[16]

The good news is, now that the relocation is complete, the EMA is returning to its business of studying and promoting effective medical practices, one of which includes the treatment of rare diseases. The EU has about 25 million rare disease patients, and the EMA will now be working on the further development of orphan-designated medicines.[17]

Clinical Trials and Drug Testing

Companies that used to conduct clinical trials in the UK may need to transfer operations into an EU member state before the transition period ends,[18] which will take time and could have similar consequences to the staff loss experienced by the EMA moving location.

The EFPIA has suggested that the EU be allowed to recognize UK-based drug testing for the time being, until this testing can take place in the EU.[19] Since more than 4,800 UK-EU clinical trials took place between 2004 and 2016[20] and given that 1,500 current registered clinical trials in the EU have a UK based sponsor,[21] future collaboration on clinical trials might be the best option.

Hoping for a Soft Brexit

Unless a 'soft Brexit' deal is passed instead of a no-deal, which would allow the UK to maintain some regulatory consistency with the EU, pharmaceutical companies should both expect and be prepared to deal with a certain amount of upheaval, especially where regulatory approvals are concerned.

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The current review period has seen a number of changes in the regulation of medicines and regulatory guidance in the EU, International markets and the USA.

United States of America

CMC information for human gene therapy INDs

This guidance finalizes the draft guidance of the same title dated July 2018 and supersedes the document entitled "Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)," dated April 2008 (April 2008 guidance). The field of gene therapy has progressed rapidly since the previous April 2008 guidance. Therefore, FDA is updating that guidance to provide current FDA recommendations regarding the CMC content of a gene therapy IND. This guidance is organized to follow the structure of the FDA guidance on the Common Technical Document (CTD).

The CMC information submitted in an IND describes the sponsor's commitment to perform manufacturing and testing of the investigational product as stated. FDA acknowledges that manufacturing changes may be necessary as product development proceeds, and information amendments should be submitted to supplement the initial information submitted for the CMC processes. The CMC information submitted in the original IND for an early phase study may be limited, and therefore, the effect of manufacturing changes, even minor changes, on product safety and quality may not be sufficiently understood. Thus, if a manufacturing change could affect product safety, identity, quality, purity, potency, or stability, applicants should submit the manufacturing change for FDA review prior to implementation.

FDA Continues Strong Support of Innovation in Development of Gene Therapy Products

This is a pivotal time in the field of gene therapy as the FDA continues its efforts to support innovators developing new medical products for Americans and others around the world. To date, the FDA has approved four gene therapy products, which insert new genetic material into a patient's cells. The agency anticipates many more approvals in the coming years, as evidenced by the more than 900 investigational new drug (IND) applications for ongoing clinical studies in this area. The FDA believes this will provide patients and providers with increased therapeutic choices.

In that spirit, today, the FDA is announcing the release of a number of important policies: six final guidances on gene therapy manufacturing and clinical development of products and a draft guidance, 'Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations'.

Applications Affected by the Reorganization of the Office of New Drugs

The approved restructuring of the Office of New Drugs (OND) creates offices that align interrelated disease areas, and divisions with clearer and more focused areas of expertise. As a result, the names of OND's offices and divisions have changed. If there is a change in signatory, or point of contact for applications currently under review, then sponsors will be notified. However, at the start of each phase, FDA encourages sponsors to search within the provided Excel file for applications currently under review that may be affected by the reorganization.

Clinical immunogenicity considerations for biosimilar and interchangeable insulin products

The purpose of this draft guidance is to provide recommendations to applicants regarding whether and when comparative clinical immunogenicity studies may be needed to support licensure of proposed biosimilar and interchangeable recombinant human insulins, recombinant human insulin mix products, and recombinant insulin analog products that are intended for the treatment of patients with Type 1 or Type 2 diabetes mellitus (collectively described as "insulin products").

In this guidance, FDA describes its updated thinking that, generally, if a comparative analytical assessment based on state-of-the-art technology supports a demonstration of "highly similar" for a proposed biosimilar or interchangeable insulin product, there would be little or no residual uncertainty regarding immunogenicity; in such instances, the proposed biosimilar or interchangeable insulin product, like the reference product, would be expected to have minimal or no risk of clinical impact from immunogenicity. In such instances, a comparative clinical immunogenicity study generally would be unnecessary to support a demonstration of biosimilarity or interchangeability. For some proposed biosimilar or interchangeable insulin products, a comparative clinical immunogenicity study may still be needed to address residual uncertainty regarding immunogenicity. For example, such a study would be needed to address uncertainty raised by, among other things, differences in certain impurities or novel excipients, but that would be a case-by-case scientific determination in the context of individual applications.

Transdermal and topical delivery systems - product development and quality considerations

This draft guidance provides recommendations to applicants and manufacturers of transdermal and topical delivery systems (TDS) regarding the pharmaceutical development and quality information to include in new drug applications (NDAs) and abbreviated new drug applications (ANDAs). Specifically, the guidance discusses FDA's current thinking on product design and pharmaceutical development, manufacturing process and control, and finished product control. It also addresses special considerations for areas where quality is closely tied to product performance and potential safety issues, such as adhesion failure and the impact of applied heat on drug delivery.

Transdermal delivery systems are designed to deliver an active ingredient (drug substance) across the skin and into systemic circulation, while topical delivery systems are designed to deliver the active ingredient to local tissue. Both delivery systems present similar manufacturing and quality control concerns and similar risks to patients. TDS can be broadly divided into matrix type and liquid or gel reservoir type delivery systems.

- ***Matrix type TDS*** contain one or more active ingredients dissolved or partially suspended in a mixture of various components, including adhesives, penetration enhancers, softeners, and preservatives, and are typically manufactured using solvent, hydrogel, or hot melt-based practices.
- ***Reservoir type TDS*** similarly contain a variety of components in liquid or semi-solid form; however, reservoir type TDS utilize a heat-sealed area to entrap the active gel between the backing membrane and a microporous membrane. Because of the inherent failure modes and safety risks associated with the reservoir TDS, FDA recommends TDS manufacturers and applicants focus development efforts on matrix type TDS.

Europe

EDQMT

EDQM launches new Pharmeuropa website

EDQM has developed a new *Pharmeuropa* website, which went live on 23 January 2020.
The new website has been redesigned and now has more features that are expected to improve the user experience. For example:

- single sign-on with other EDQM websites using the same authentication database, including Ph. Eur. online and PaedForm;
- improved navigation using standard web browser functionality;
- tablet and smartphone friendly;
- improved search query management;
- a notification tool enabling users to set alerts for important information for their business, based on monograph numbers or Ph. Eur. groups of experts.

All users will have to register for access, even those who had access to the previous site.

New approach to extraneous agents testing of immunological veterinary medicinal products (IVMPs)

During its 164th session on 18 June 2019, the European Pharmacopoeia Commission adopted 43 texts related to its new approach to extraneous agents testing of immunological veterinary medicinal products (IVMPs). The new approach constitutes a move away from the description of detailed methods towards greater flexibility and allowing tailoring to individual product needs. From starting material to final product, users will now have to follow an overall risk-management approach to ensure they apply the best testing strategies in the context of a consistent manufacturing process.

Pharmeuropa 31.4 released

53 drafts have been published in Pharmeuropa 31.4. Comments were to be provided by 30 Dec 2019.

Comments made after adoption of the text and/or publication in the Ph. Eur. will be too late to be considered. Users may then be in a position where their product is not compliant with the Ph. Eur. monograph, which is a legal standard in Europe. This could ultimately lead to a situation where a product can no longer be marketed in Europe.

Pharmeuropa 32,1

All new texts and texts that have undergone technical revisions are published in Pharmeuropa for public consultation. The deadline for comments is 31 March 2020.

European Paediatric Formulary online

Launched by the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) and the European Pharmacopoeia Commission, the European Paediatric Formulary project is carried out by experts of a dedicated working party. The aim is to bring together, for the first time, formulations of appropriate quality from all around Europe to allow pharmacists and clinicians to prepare paediatric treatments when no licensed alternative is available.

The formulary can be accessed free of charge.

EMA

Revised Q&A on impact of EU-USA MRA on marketing authorisation applications and relevant variations

Q&A 1, relating to 'How does the EU-USA Mutual Recognition Agreement (MRA) affect marketing authorisation applications or variations', has been revised.

Updated Q&A on "Information on nitrosamines for marketing authorisation holders"

This very important Q&A document was updated on Dec 20 2019.

Q&As subject to update were:-

#1 Are all products to be reviewed?

#6 What limits will apply for nitrosamines detected in any products??

#11 What limits will apply for nitrosamines detected in any products?

#12 What are the currently identified root causes for presence of nitrosamines?

New Q&As are :-

#13 What is the approach for new and ongoing marketing authorisation applications (MAA)?

#14 Are biological products containing excipients potentially at risk of contamination with Nitrosamines in the scope of the review?

#15 What to do if after completing step 1 and /or step 2 new information on new potential root causes is identified?

#16 What limits will apply for nitrosamines in medicinal products based on lifetime and less than lifetime use?

Readers attention is drawn to this document which should be urgently and carefully reviewed for scope, methodology and timelines.

[Note that as well as the involvement of e.g. sodium Nitrite, recovered solvents etc., that under section 12 point 8 "Use of certain packaging materials" that nitrosamine contamination has been observed by one MAH in a finished product stored in blister. The MAH has hypothesised that the lidding foil containing nitrocellulose printing primer may react with amines in printing ink to generate nitrosamines, which would be transferred to the product under certain packaging process conditions." MBH.]

UK withdrawal from the EU on 31 January 2020

The United Kingdom formally left the European Union on 31 January 2020 and became a third country to the EU. On 1 February 2020 a transition period started which is due to end on 31 December 2020. During the transition period, EU pharmaceutical law as laid out in the 'Acquis Communautaire' will continue to be applicable to the UK, meaning that pharmaceutical companies can continue to carry out activities in the UK until the end of the year. Companies have until 31 December 2020 to make the necessary changes to ensure that their authorised medicines comply with EU law and can remain on the EU market. Marketing authorisation holders/ applicants can still be established in the UK and Qualified Persons for Pharmacovigilance (QPPVs) and pharmacovigilance system master files (PSMFs), as well as quality control testing sites, can still be based in the UK until the end of 2020.

As of 1 February 2020, no one who represents the UK, or is appointed or nominated by the UK can participate in meetings of EMA's scientific committees, working parties or the Agency's Management Board.

Updated Brexit-related guidance for companies has also been published.

European authorities working to avoid shortages of medicines due to Brexit – updated Q&A

The relationship between the UK and the EU after the transition period started which is due to end on 31 December 2020 is currently unknown and will be determined by future negotiations. During the transition period, European Union law in its entirety will continue to apply to the UK, meaning that pharmaceutical companies can continue to carry out activities in the UK as before until the end of the transition period. However, all interested parties should be mindful of legal repercussions when the transition period ends. To ensure that medicines can continue to be supplied in the EU after this period, companies carrying out certain activities in the UK will need to make changes to comply with EU law.

Availability / shortages of medicines

Since April 2019, the task force has been running a pilot programme on establishing a Single Point of Contact (SPOC) network to improve information sharing between Member States, EMA and the European Commission on important medicine shortages of human and veterinary medicines and to coordinate actions to help prevent and manage shortages. This includes information sharing on alternative medicines that are available in other Member States.

The first phase of the pilot ran from April to August 2019 to test the functioning and usefulness of the information exchange via the SPOCs. During this phase, 24 Member States used the SPOC system and circulated 52 notifications of shortages.

The task force plans to run a second phase of the pilot in 2020, to test the criteria for identifying cases deserving EU-wide coordinated action and for network alerts of upcoming public communications that could have a high impact on patients.

The task force will publish more information after completion of the second phase of the pilot.

International collaboration on GMP inspections – manufacturers of sterile medicines.

In December 2019, EMA and its European and international partners launched a pilot programme to share information on GMP inspections of manufacturers of sterile medicines located outside the participating countries and to organise joint inspections of manufacturing sites of common interest.

The products in scope include sterile medicines for human use of chemical origin and certain therapeutic biotechnology - derived products, such as monoclonal antibodies and recombinant proteins.

Vaccines, cell and gene therapies and plasma-derived pharmaceuticals are currently out of the scope of this pilot.

For the terms of reference, objectives and full scope, see:

Participating authorities and organisations include:

- EU Member States (France and the United Kingdom);
- the United States FDA;
- the Australian TGA;
- Health Canada
- the Japanese PMDA;
- the World Health Organization (WHO).

The pilot will last for a minimum of two years. After this period, participating authorities will assess the programme and determine the next steps.

This initiative builds on the success and experience with the API inspection programme.

Substances considered as not falling within the scope of Regulation (EC) No. 470/20091, with regard to residues of veterinary medicinal products in foodstuffs of animal origin

Since the implementation of Council Regulation (EEC) No. 2377/90, the CVMP has deliberated on many substances (including excipients, adjuvants and preservatives) to be used in veterinary medicinal products intended for food producing species, and regularly receives requests (either scientific advice or ad hoc requests) to consider whether such substances fall within the scope of the MRL regulation. The substances for which the CVMP has concluded that no MRL evaluation is required are listed in the CVMP publication "Substances considered as not falling within the scope of Regulation (EEC) No. 2377/90" (EMEA/CVMP/046-00), also often referred to as the 'out of scope list'. The list also includes a small number of compounds that do not fall within the categories of excipients, adjuvants or preservatives but are natural substances essential for life or are biologically active constituents. Due to the nature of these specific compounds the CVMP considered that an evaluation for the establishment of maximum residue limits would not be appropriate. Following the implementation of Regulation (EC) No. 470/2009 there was a need to update the background information and legal references included in the document containing the 'out of scope list'. This document performs that function and supersedes the CVMP publication Substances considered as not falling within the scope of Council Regulation (EEC) No. 2377/90. The list includes all the substances included in the superseded document. It should be noted that this list of substances is in no way exhaustive and includes only substances for which requests in this respect were made to CVMP by a company or a national authority

Tripartite meeting held to discuss regulatory approaches for the evaluation of antibacterial agents

This fourth tripartite meeting between the EMA, the US FDA and the Japanese PMDA discussed further alignment on clinical trial designs for key indications for antibacterial drugs for which convergence has not yet been reached. They agreed that data from contemporary clinical trials would be pivotal in defining the most suitable way forward. They also expanded the discussions to include antifungal agents, an area which is also affected by growing antimicrobial resistance and where clinical development programs can be challenging.

The agencies discussed:

- methods to facilitate obtaining paediatric clinical data and utilisation of modelling and simulation. Paediatric development is an important aspect in the development of anti-infective products;
- differences in test methods and derived interpretive criteria for susceptibility testing in the European Union, Japan and the Unites States. To facilitate multi-regional anti-infective medicine development, communication and collaboration among scientific and public health bodies involved in such activities are key and options for harmonisation are strongly encouraged;
- clinical trial considerations for new treatment modalities such as monoclonal antibodies and other non-traditional therapies for the treatment and/or prevention of infectious diseases. The need to work together to facilitate new approaches and to aim for convergence was recognised.

The agencies plan to meet again in 2020. They also plan to publish the outcome of their discussions, in a scientific journal.

Regulators' Advice Can Make a Difference: European Medicines Agency Approval of Zynteglo for Beta Thalassemia

Zynteglo is a gene therapy for the treatment of patients with beta-thalassemia, a rare inherited blood

condition that causes severe anaemia. Some patients can be cured through a stem cell transplant from a healthy donor. However, patients who have no matched family donor miss out. For them, Zynteglo could be a game changer. Using a lentiviral viral vector, it adds functional copies of a modified β-globin gene into a patient's own stem cells, thereby addressing the underlying genetic cause of the disease.

Ground-breaking therapies such as Zynteglo present specific challenges for those who assess their benefits and risks for the initial authorisation and those who assess their value as a basis for pricing and reimbursement decisions. Continuous dialogue throughout the development of the medicine, without compromising the impartiality of the assessment at the marketing-authorisation application stage, can help overcome these challenges.

In the case of Zynteglo, the medicine benefited from PRIME, EMA's platform for early and enhanced dialogue with developers of promising new medicines that address an unmet medical need and several interactions with EMA's scientific advice office with input from patients' representatives.

An article, accessible via open access in Clinical Pharmacology & Therapeutics, describes how such interactions led to a more robust application package to demonstrate the medicine's benefits and risks, which in turn allowed accelerated assessment. In the article, the authors describe some of the specific clinical and manufacturing process issues which were identified and how these were overcome. They also show that early accelerated approvals are only possible if a robust post-approval plan is defined at the marketing authorisation stage.

[Perhaps not a typical example but it is yet another example of how early dialogue with a regulator can speed up an approval process, whether it is for a new product, a process or manufacturing facility.

In these times of significant developments in the field of medicines and their sources plus novel manufacturing techniques such early dialogue is surely Good Practice [GxP]. MBH]

Dutch Authorities hand over final building to EMA in Amsterdam

On 15 November the Dutch authorities handed over to EMA its newly built tailor-made premises, located in the Zuidas area of Amsterdam. Staff moved into their new offices and workspaces in January 2020.

EMA Management Board: highlights of December 2019 meeting

Executive Director Guido Rasi stressed the challenges that the Agency now faces in reinitiating its activities following three years of relocation and Brexit and postponed investment into business-critical infrastructure. In the meantime, important new demands have been placed on the Agency that will need to be prioritised, such as the implementation of the new legislation for veterinary medicines and on medical devices.

The Agency now has an available workforce of 775 which is significantly less compared to end 2017 when EMA's relocation plans took shape.

In defining its work programme for 2020 and beyond, EMA will focus on the core activities identified in the last phase of business continuity as a baseline and will prioritise additional tasks depending on available resources. The Agency will continue to monitor staff levels and review whether additional activities can be relaunched in June 2020.

To help the Agency make best use of available resources and be best prepared for future challenges, EMA is currently conducting an in-depth review of its organisation.

This future-proofing exercise will help EMA to strengthen its ability to perform important new activities together with the European regulatory network and to tackle important challenges ahead such as big data, digitalisation and new scientific methods and technologies.

Highlight topics from the meeting include:-

EMA budget for 2020

The 2020 budget is set at EUR 358 million, a 3.3% increase on 2019.

EU cooperation on medicines' availability

The Board heard an update on the outcome of the first phase of a pilot on the EU SPOC (single point of contact) network for cooperation on availability of human and veterinary medicines.

A second phase is foreseen for 2020 during which additional responsibilities of the SPOCs will be tested which are expected to improve the handling of shortages. Before moving to the second phase, however, it is important to ensure that necessary resources can continue to be made available by EMA and the national authorities in the Member States.

More information will be published once the second phase of the pilot is completed.

Update on the EU IT systems required by the Clinical Trial Regulation

The Board endorsed the outcome of the 'audit readiness assessment' and endorsed the proposal to commence the audit in December 2020.

In the first few months of 2020, product owners will work with EMA and the IT supplier to perform the analysis and design of the items that have been prioritised as still needing to be fixed/developed before the audit can begin. The approach will be carried out in a way that ensures efficient delivery.

Handling new information on nitrosamine presence in medicines

The European medicines regulatory network has agreed to reinforce the

use of interim limits for the evaluation of cases where nitrosamines are identified, in line with the report issued by the Agency on the sartan review. Should the interim limits be exceeded this will be handled through the EU network's existing rapid alert systems. The Board welcomes the cooperation on the issue that is already ongoing at European level and encourages continued discussion with regulators from outside the EU.

Other meeting highlights were:-

- Mandatory use of international standard for reporting side effects to improve safety of medicines
- HMA-EMA Joint Big Data Taskforce Report
- Key principles and roadmap on electronic product information (ePI)
- Key principles and roadmap on electronic product information (ePI)

Post-authorisation procedural advice for users of the centralised procedure

Grouping of variations: Q&A – This updated document lists questions that marketing-authorisation holders (MAHs) may have on grouping of variations. It provides an overview of the EMA's position on issues that are typically addressed in discussions or meetings with MAHs in the post authorisation phase. Revised topics are marked 'New' or 'Rev.'.

Q&A on comparability considerations for advanced therapy medicinal products (ATMP)

This document addresses questions on how to demonstrate comparability for gene and cell-based medicinal products following change to the manufacturing process or due to introduction of additional manufacturing sites.

FAQ about parallel distribution

This page lists questions about parallel distribution of human & veterinary medicines. The information is available as Q&As, which the EMA revises as necessary.

International

Australia – Therapeutic Goods Administration (TGA)

Safety review of coumarin in topical listed medicines

Coumarin is a naturally occurring chemical found in a number of food products such as cinnamon and tonka bean. Coumarin is currently permitted for use as a listed medicine; however, it is only permitted for use as an active homoeopathic ingredient (with a maximum concentration of 0.001%). During a review of listed sunscreen products, the TGA became aware that coumarin was being used as a fragrance in sunscreen and other topical listed medicines however was not on the Therapeutic Goods (Permissible Ingredients) Determination ('the Determination'). Therefore, the TGA conducted a preliminary safety review to determine whether coumarin was appropriate for use in listed medicines and sunscreens as a fragrance ingredient.

The review was unable to establish a safe concentration limit for the topical use of coumarin, and identified some safety concerns such as liver injury, skin sensitisation, and populations at greater risk such as children and pregnant/ breastfeeding women.

Additional data was provided which addressed some of the safety concerns in the preliminary safety review. This information has been considered and used to finalise the safety review.

The additional data provided has been considered and incorporated into the final safety review. In particular, data for reproductive and developmental toxicity was able to address the safety concerns regarding coumarin in pregnancy and breastfeeding. However, concerns regarding the use of coumarin in children remains outstanding. As sunscreens may be used by the entire family, sunscreens containing coumarin will need to specify they should only be used by adults. This requirement will also apply to any other topical listed medicines.

The safety review establishes that the appropriate tolerable daily limit for coumarin exposure from all sources (including diet, cosmetic products and sunscreens) is 0.1 mg/kg bodyweight. The IFRA standard proposes a limit of 0.3% coumarin in products for use on the body. A sunscreen containing coumarin at this level would provide 6 mg/kg bodyweight of coumarin (60-times the tolerable daily limit) when used as recommended for a full-day. A sunscreen containing 0.001% coumarin used in the same way would provide 0.02 mg/kg bodyweight (this is 20% of the tolerable daily limit). In the absence of a reliable estimation of Australian intake of coumarin from dietary and cosmetic sources, this lower limit is considered to be more appropriate for low risk listed medicines. As such, the requirements for listed medicines will specify that topical products may not exceed a concentration of 0.001% coumarin.

Sponsors of existing listed medicines and sunscreens will have until 2 March 2021 to bring their products into compliance.

Consultation: Draft standards for faecal microbiota transplant (FMT) products

TGA is seeking comments from interested parties on proposed standards for faecal microbiota transplant (FMT) products in Australia. This is a new area of regulation for TGA from 2020.

Reforms to the generic medicine market authorisation process: implementation update

In early 2019, TGA consulted on proposed reforms to the generic medicine market authorisation process. In response to the feedback received, TGA implemented the following changes:

- Reduced requirements for use of overseas reference products in bioequivalence studies.
- Options to use new internationally aligned templates for summarising bioequivalence or biowaiver study data.

Uniform recall procedure for therapeutic goods (URPTG)

A new version of the Uniform Recall Procedure for Therapeutic Goods (URPTG) (V2.2, December 2019) has been implemented, with effect from 12 December 2019.

This version updates V2.1 to include:

- additional clarity on the provision of surgeon contact details for implanted therapeutic goods
- amendments related to the online notification of recall and non-recall actions
- removal of the placeholder referring to the National Patient Contact Principles for Patients with Implanted Medical Devices subject to Hazard Alerts
- a second example template for the sponsor's customer letter.

This version also includes a number of other minor editorial amendments.

Medicinal cannabis manufacture

This guidance is for manufacturers of medicinal cannabis products. It outlines and provides information on:

- manufacturing license and certification requirements
- differences between Therapeutic Goods Administration (TGA) and Office of Drug Control (ODC) requirements
- TGA interpretation and expectations for compliance with specific sections of the current PIC/S Guide to GMP.

Export of therapeutic goods from Australia

The TGA is seeking comments from interested parties on an update to guidance for

- Export of medicines from Australia
- Export certification for medical devices

Comments were to be submitted by 3 Feb 2020

PIC/S

Draft PIC/S Recommendation on How to Evaluate / Demonstrate the Effectiveness of a Pharmaceutical Quality System in relation to Risk-based Change Management

PIC/S has published on a draft basis a Recommendation on How to Evaluate / Demonstrate the Effectiveness of a Pharmaceutical Quality System in relation to Risk-based Change Management (PI 054-1 (Draft 1)) developed by the PIC/S Expert Circle on Quality Risk Management (QRM).

This draft Recommendation will be applied on a 6-month trial basis by PIC/S Participating Authorities.

The purpose of this draft document is to provide guidance on evaluating and demonstrating the effectiveness of a PQS in relation to risk-based change management. This is in recognition of the fact that the PIC/S GMP Guide requires companies to demonstrate the effectiveness of their PQS and to apply quality risk management (QRM) principles to change control activities. Further information on the background to this Recommendation and the anticipated benefits of this guidance are provided in PIC/S Concept Note (PS/INF 88/2019).

This draft document is not open for comments by industry.

PIC/S events in Toyama, Japan, 11-15 November 2019

PIC/S Committee met on 11-12 November 2019 in Toyama (Japan). The meeting was followed by the PIC/S annual training Seminar on 13-15 November 2019. The topic of the seminar was "Quality Assurance of Sterile Medicinal Products - Annex 1".

The press release regarding these events is available in newsletter format on the PIC/s website.

Products

First oral GLP-1 treatment for type 2 diabetes

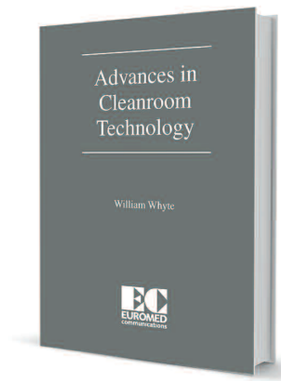
EMA's human medicines committee (CHMP) has recommended granting a marketing authorization in the European Union (EU) for Rybelsus (semaglutide) for the treatment of adults with insufficiently controlled type 2 diabetes to improve glycaemic control as an adjunct to diet and exercise. It is the first glucagon-like peptide (GLP-1) receptor agonist treatment - a class of non-insulin medicines for people with type 2 diabetes - developed for oral use, providing patients with another option to treat the disease without injections. The active substance in Rybelsus, semaglutide, acts in the same way as the incretin hormone GLP1: it reduces blood glucose by stimulating pancreatic secretion of insulin and lowering the secretion of glucagon (a hormone that works to raise blood sugar concentration) when blood sugar is high. The opinion adopted by the CHMP is an intermediary step on Rybelsus's path to patient access. The CHMP opinion will now be sent to the European Commission for the adoption of a decision on an EU-wide marketing authorisation.

This review is produced by Malcolm Holmes an independent pharmaceutical consultant. For further information on these and other topics we suggest you refer to the websites of relevant regulatory bodies and to current and past editions of "GMP Review News" published by Euromed Communications.

Euromed books

Books on pharmaceutical management and clinical research

EUROMED communications



Advances in Cleanroom Technology

William Whyte

ISBN 978-0-9956666-5-8

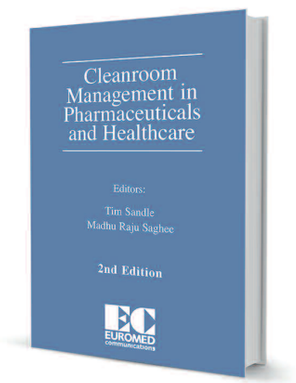
This book is based on the author's work, published over the last sixteen years to advance knowledge of cleanroom technology. Thirty-four articles are collected and divided into seven sections that cover common themes, with helpful introductions. The themes include the history of cleanrooms and operating theatres; risk assessment; ventilation design and air supply rates; required cleanroom standard for specified product contamination; and the dispersion, transfer and deposition of contamination.

At over 500pp, this book is a comprehensive and valuable source book for anyone involved in the design, testing and operation of cleanrooms.

Cleanroom Management in Pharmaceuticals and Healthcare

Edited by Tim Sandle and Madhu Raju Saghee

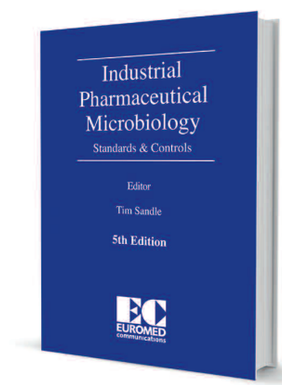
ISBN 978-0-9573491-6-2



Everything you need to know about the operation and management of cleanrooms.

In 26 Chapters and over 600 pages this book provides a unique tool to help you achieve regulatory compliance. It first creates a foundation in history and established practice and then helps you understand how state of the art technology and engineering solutions can deliver the best practice and so provide reliable systems performance.

An essential read for practitioners in cleanroom technology.



Industrial Pharmaceutical Microbiology:

Standards &Controls – 5th Edition

Edited by Tim Sandle

ISBN 978-0-9573491-1-7

The contamination control of pharmaceutical and healthcare environments and processes, together with pre-clinical drug development labs, requires a far more holistic approach than simply choosing technologies and disinfectants. Today the microbiologist is expected to understand industrial processes and cleanrooms, and how to effectively evaluate microbial risks to products from personnel and processes.

Includes 25 chapters, 23 authors and over 600 pages of text.
With many illustrations, tables and diagrams

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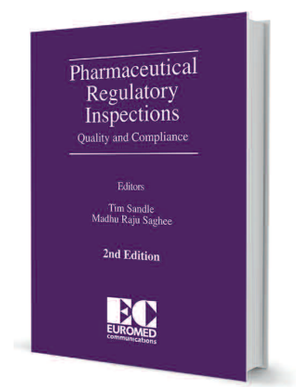
*Foreword by Peter D. Smith**

ISBN 978-1-899015-89-4



A unique and comprehensive guide to ensure regulatory compliance and success in pharmaceutical regulatory inspections. In over 600 pages and fourteen chapters this unique book provides a focussed account of regulatory issues from pre-approval inspections and the inspection itself to post inspection and maintaining compliance. This is a book that every pharmaceutical company will wish to study before and during any inspection process to ensure a successful outcome.

*Vice President, Strategic Compliance, PAREXEL Consulting, USA

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bottled brown

Trying to do good

Are you a comparatively humble person who believes that the world can be made a better place, tries to do good and is made happy by evidence that it has been done? If you are, you are a "meliorist" according to the Nobel Laureate scientist Peter Medawar (1915 – 1987).

Ends and means

You wish to improve drug therapy such as for ovarian cancer. It remains so common that the lifetime likelihood for a woman is one in about 50; I will revisit that disease. The financial model for the British pharmaceutical industry is that a company profits from a new medicine during the patent period and that pays for discovery and development costs of products that, otherwise, might not be invented. Government, during negotiations, achieves some market control by deciding how much the NHS is willing to pay, or similar means. For example, for wet age-related macular degeneration (AMD), the regulatory authority in the UK only licensed Lucentis and Eylea. However, the National Institute for Clinical Excellence (NICE) and the high court (supreme court appeal pending) ruled that the NHS could substitute Avastin — 24 times cheaper. That enables NHS treatment of more patients for the same money but perhaps patients and clinicians may become uncertain whose advice they can trust.

Of course, any (non-charitable) commercial undertaking requires some profit to survive. Both parties negotiating (the industry and government) sincerely share the same honourable desired "end (result)": improvement of people's health but use different means to achieve that end. Arguably, another perspective is that the "good" of treating more patients short-term becomes the "bad" of improved therapies being unavailable long-term.

Uncertainty

Another complication churns. Companies may be accused of doing harm and suffer expensive litigation. For example, talc has been claimed to be contaminated with asbestos. This contamination has always been potentially present; geologically, the two minerals are often close together. Courts have awarded damages following claims that asbestos-contaminated talc, used genitally, increases the risk of ovarian cancer by 33%. Court cases stimulate such eye-catching headlines. They presumably boost media circulation. In fairness, academic researchers, who must find funding, "the beggars of the universities", also make as much as they can of their results. However, simple arithmetic, assumptions and approximations allow a restatement of that relative risk as an absolute risk of an extra one in about 2,421. Then, over the oft-quoted five-year, not lifetime, period, a rectangular pictogram of 1,000 icons of women shows, by shading, that only about 0.41 of one woman is affected and, crucially, that all the rest are not. That understanding can be taken in at a glance of the visual field. The informed patient could then decide whether the likelihood was big enough for concern; individuals tolerate risk differently. The 2015 edition of the British National Risk Register of Civil Emergencies was the last to quantify likelihoods. It suggested that at least a hundred times more likely was a flu pandemic or severe space weather such as the "Carrington event" (1859). That caused chaos in telegraph communication. It could in today's electronically-interconnected global world including intercontinental just-in-time fragile industrial supply chains.

Some implications are worth highlighting. Although the British government has power to choose to invest or not, other countries may be willing to pay more. Taxation and intellectual property rights vary across countries. Private individuals also leap to pay especially if novel medicaments become available. Imagine block-buster "Dorian Gray" or intelligence-boosting drugs. You can play your part in safeguarding that your company is careful and fair in its data presentation, so making the world a better place.

Malcolm E Brown

events

APRIL

1– 2 April 2020 – London, UK
13th European Biosimilars Congress 2020
https://biosimilars-biologics.pharmaceuticalconferences.com/europe/

12–14 April 2020 – Lisbon, Portugal
5th International Conference on Nanomedicine, Drug Delivery, and Tissue Engineering
https://nddte.com/

20–22 April 2020 – Munich, Germany
14th International Pharmaceutical and Medical Device Compliance Congress
https://www.internationalpharmacongress.com/

21–22 April 2020 – Berlin, Germany
Visual Inspection Forum
https://www.pda.org/global-event-calendar/event-detail/visual-inspection-forum

21–23 April 2020 – Berlin, Germany
Global Pharmaceutical Regulatory Affairs Summit
https://informaconnect.com/global-pharmaceutical-regulatory-affairs/

29 April–1 May 2020 – Washington, DC, USA
17th Annual Pharmaceutical Compliance Congress
http://www.cbinet.com/conference/pc20001

29 April–1 May 2020 – Oxon Hill, MD, USA
World Orphan Drug Congress USA 2020
https://www.terrapinn.com/conference/world-orphan-drug-congress-usa/index.stm

MAY

13 May 2020 – London, UK
4th Annual Global Clinical Trials Connect 2020
https://london.eventful.com/events/4th-annual-global-clinical-trials-connect-2020-/E0-001-129088129-5

18–19 May 2020 – Berlin, Germany
30th Annual European Pharma Congress
https://europe.pharmaceuticalconferences.com/

18–19 May 2020 – Berlin, Germany
22nd Annual European Pharma Congress
https://www.clocate.com/conference/annual-european-pharma-congress/64205/

18–20 May 2020 – Brussels, Belgium
Clinical Trial Supply Europe
https://10times.com/clinical-trial-supply-europe

25–26 May 2020 – Osaka, Japan
26th World Congress on Nanomaterials and Nanotechnology
https://nanomaterials.materialsconferences.com/

29–30 May 2019 – Istanbul, Turkey
27th International Conference on Nanomedicine and Nanomaterials
https://www.vydya.com/events/nano-med-2020/

29–30 May 2020 – London, UK
14th World Drug Delivery Summit
https://www.clocate.com/conference/world-drug-delivery-summit/55121/

JUNE

1–3 June 2020 – Boston, MA, USA
2020 ISPE Biopharmaceutical Manufacturing Conference
https://ispe.org/conferences/2020-ispe-biopharmaceutical-manufacturing-conference

2–3 June 2020 – Montreal, Canada
Pharmaceutical Compliance Congress Canada
https://informaconnect.com/pcc-canada-pharmaceutical-compliance-congress/

3–4 June 2020 – Boston, MA, USA
2020 ISPE Continuous Manufacturing Workshop
https://ispe.org/conferences/2020-ispe-continuous-manufacturing-workshop

9–10 June 2020 – Dublin, Ireland
Quality and Regulations Conference
https://www.pda.org/global-event-calendar/event-detail/quality-and-regulations-conference

18–19 June 2019 – Arlington, VA, USA
3rd Annual Compounding Pharmacy Compliance
https://informaconnect.com/compounding-pharmacy-compliance/

24–25 June 2020 – Washington, DC, USA
2020 PDA Advanced Therapy Medicinal Products Conference
https://www.pda.org/global-event-calendar/event-detail/2020-pda-advanced-therapy-medicinal-products-conference

24–25 June 2020 – Brussels, Belgium
2020 PDA Europe Advanced Therapy Medicinal Products Conference
https://www.pda.org/global-event-calendar/event-detail/advanced-therapy-medicinal-products