DBA

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The Journal of David Begg Associates

Issue 7 Autumn 2007

The trouble with air!

Why air removal is critical for effective steam sterilisation

David Begg associates

The Pharmaceutical Training Experts

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welcome

A fond farewell

**Bob Pietrowski,
Managing Partner
David Begg
Associates**

The more observant of you will have noticed that there is a different photograph at the side of this page.

After 20 years at the helm of David Begg Associates, Mike Bowsher decided to retire from the business this summer. In those 20 years, Mike has overseen the growth of DBA from a two man operation into one of the top pharmaceutical consultancies in Europe. We are all deeply indebted to him for his vision and leadership over that period and we wish Mike and his wife Gloria a very long and happy retirement.

For the rest of us here at DBA, it is business as usual. We will carry on working tirelessly to provide you with top class training courses and practical, cost-effective advice and consultancy to help you to succeed in your activities. To do that, however, we need your help. Please continue to send us your suggestions for new courses, new venues and any other ideas you have on how we can help you further.

We at DBA are committed to helping you to achieve your personal goals and be the best you can be, and we all look forward to working with you in the years to come.

Bob Pietrowski
Managing Partner

Tech Talk

Why is it that some EU regulatory agencies regard this as such a big issue, whilst others fail to see the importance?

Why is air removal so critical to effective steam sterilisation?

There are many examples of differences in detail between EU and US GMP expectations, but one of the biggest and most important concerns air removal in steam sterilisation. Why is it that some EU regulatory agencies regard this as such a big issue, whilst others fail to see the importance?

The Importance of Air Removal

To achieve effective steam sterilisation, dry saturated steam must contact the surfaces to be sterilised so that energy can be transferred. It follows, therefore, that nothing must come between the steam and the surface to be sterilised. Herein lies our major challenge. Most of the equipment we seek to sterilise (filters, tubing, vessels, filling needles, etc) contain vast quantities of air. If this air is not removed, then it can act as an insulating barrier between steam and equipment and thus compromise the sterilising process.

Thus, in the case of equipment sterilisation, the key to effective sterilisation is…

- **total removal of air (and condensate)**
- **complete replacement of air by dry saturated steam**

Hence the emphasis on air removal!

Methods of Air Removal

Equipment is generally sterilised by the use of a so-called "porous load" autoclave cycle, whereby air is removed from the autoclave chamber and load by pulling a vacuum and replacing the vacuum by steam. Generally speaking, a single vacuum pulse, no matter how long in duration, is unlikely to achieve total air removal; a series of vacuum pulses will be necessary. The number and duration of pulses needed to achieve efficient air removal will be determined by the nature of the equipment to be sterilised and the way it is wrapped. Thus, a 50 litre vessel with a small vent filter attached to it via 1m of 10mm diameter silicone tubing represents a huge challenge to the air removal capability of the autoclave as all the air must be drawn out of the vessel and tubing via the small vent filter. Whilst it may be relatively easy to remove air from the autoclave chamber (as measured by the controlling pressure sensor) it will be much more difficult to remove all the residual air from the equipment. Excessive wrapping only exacerbates the problem.

That is why it is so important to optimise the pre-sterilisation phase of the autoclave cycle to ensure…

- **total air removal effective**
- **heating of the load**

Air may be removed by a series of sub-atmospheric (negative) pulses, which draw out air by vacuum and then replace the vacuum with steam up to atmospheric pressure. Such cycles can be effective at removing air, but may be less effective at heating the load as the steam never exceeds 100°c. This problem can be overcome by incorporating a series of super-atmospheric (positive) pulses, whereby the chamber is pressurised with steam after a series of vacuum pulses and then evacuated to atmospheric pressure or below. In this way the load can be heated more

Tech talk

effectively as the steam will achieve temperatures well in excess of 100°c. Figure 1 shows a typical porous load cycle incorporating both negative and positives pulses.

If the pre-sterilisation phase of the autoclave cycle has been optimised, then transition to the sterilisation phase should result in all pieces of equipment reaching sterilisation temperature simultaneously. EN285 states that, for a typical industrial autoclave, all heat penetration thermocouples distributed within the load, should reach sterilising temperature within 30 seconds. Any delay indicates either a failure to remove air or a failure to adequately heat the load and, as such, the autoclave cycle should be considered unsatisfactory!

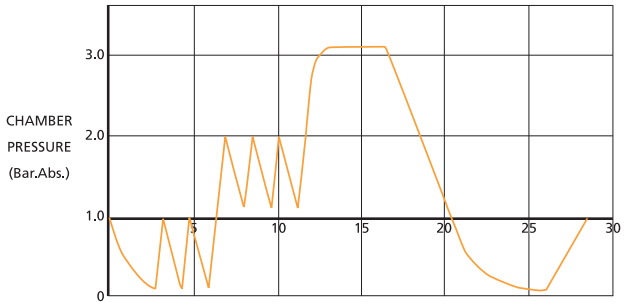

Figure 1 A typical porous load cycle incorporating both negative and positive pulses.

It is not enough simply to extend the sterilisation phase until all thermocouples achieve the desired temperature for the required time (as many companies do!) as you may not have saturated steam conditions and so will not achieve effective sterilisation. Rather, you should go back to the pre-sterilisation phase of the cycle and increase the number and/or duration of pulses to achieve the required result.

Means of Confirming Effective Air Removal

There are numerous ways of confirming effective air removal in autoclaves…

- a drain-mounted air detector
- the Bowie-Dick test (or equivalent)
- chamber leak rate test

Air detectors are relatively common on autoclaves in the United Kingdom and Ireland, but less so elsewhere. The device is fitted to the drain of the autoclave and it will not permit commencement of the sterilisation phase of the cycle until the air content in the steam leaving the chamber is below a fixed level.

The air detector alone may not be sufficiently sensitive to detect potentially significant levels of air if these are trapped within the load. Thus, a more direct test of air removal from the load is recommended – the so-called Bowie-Dick test pack. This consists of a stack of folded towels bound together and thus represents a worst case challenge air removal. In its simplest form, the test pack contains at its centre a piece of paper with a diagonal cross of autoclave indicator tape placed on it. The pack is subjected to the routine autoclave cycle and the tape cross is examined for any unevenness in colour, which indicates incomplete air removal. For qualification purposes the test can be made quantitative by placing thermocouples at the centre of the pack and on the exterior and comparing temperature difference – any depression of temperature at the centre of the pack indicates incomplete air removal. The Bowie-Dick tape test or equivalent (AMSCO DART, Lantor cube, Brown's TST pack) is typically used once a week in an empty chamber to confirm air removal capability.

Finally, it is common practice in the United Kingdom and Ireland to carry out a chamber leak rate test at the beginning of each day, using an empty, dry, warm autoclave chamber. The chamber is evacuated and then isolated by closing all valves. The ability of the isolated chamber to hold that vacuum is then assessed. A pressure rise of not more than 13mbar in 10 minutes is considered acceptable (see EN285). A greater rise indicates a leak on the chamber, for example due to a faulty door seal, which could permit entry of air to the chamber during the pre-sterilisation phase of the cycle.

Steam Quality

If we are to take such elaborate measures to ensure air removal from our loads, it follows that the steam we introduce should not contain air. This is why EN285 contains a test for **non-condensable gases** in steam. The percentage of such gases (usually air) should not exceed 3.5%.

So Much for the Theory – Is There a Problem in Practice?

Many industry representatives (and some regulators) view the concern placed on air removal by European (particularly United Kingdom and Irish) regulators as excessive. Is this just a solution in search of a problem or is there a real problem?

Last year we visited a company in North America manufacturing aseptically prepared products. The company had experienced several media fill failures, which it attributed to media contamination. The autoclave cycle used to sterilise the filter and stoppers consisted of a single vacuum pulse to remove air. The cycle had been validated using bio-indicators, but no air removal tests had ever been performed on the autoclave.

Review of the validation data showed that some thermocouples achieved sterilising temperature over 4 minutes later than the majority, indicating to us a potential air removal problem. We encouraged the company to put a Bowie-Dick test pack into the autoclave and run the same cycle – it failed catastrophically! We then encouraged the company to incorporate a series of negative and positive pulses into the pre-sterilisation phase of the cycle. After doing so…

- all Bowie-Dick tests passed
- all thermocouples in validation studies reached 121°c within 30 seconds
- all subsequent media fills passed.

Further Reading

EN285, "Sterilisation – Steam Sterilisers"
Health Technical Memorandum 2010, "Sterilisation", HMSO, London

This and many other important issues will be discussed in depth during our 4 day training course "Good Autoclave Practice", to be held in Manchester from 23 to 25 October 2007.

New DBA People

We are delighted to announce that Gary Rees joined us as an Associate Consultant on 1st September 2007.

Prior to joining DBA, Gary was Vice President, Quality and Compliance, with Wyeth, covering Europe, the Middle East and Africa.

A pharmacist by profession, Gary has over 35 years' experience of pharmaceutical manufacture, Quality Control and Quality Assurance. He has sat on numerous pharmacopoeia committees and was a member of the European Federation of Pharmaceutical Industry Associations. (EFPIA) Anti-Counterfeiting ad hoc group and so has valuable knowledge and experience in this increasingly important area.

As you can see, Gary has a wealth of practical experience to offer and we are delighted to welcome him to the DBA team. We are sure that his arrival will help us to improve the quality and breadth of services we offer.

Forthcoming Courses

What's Planned for the rest of 2007

Pharmaceutical Good Manufacturing Practice

Marriott Victoria & Albert Hotel, Manchester, UK
17 - 20 September 2007

Europe's most popular GMP course! An excellent overview of EU and US GMP regulations and expectations, plus up to the minute guidance on current "hot topics".

Course Fee £2065.00 plus VAT

Mathematics & Statistics

Qualified Person & Professional Development Training
Hilton Hotel, York, UK
17 - 20 September 2007

Perhaps the only statistics course aimed directly at the pharmaceutical industry! Given the increasing importance of PAT, Quality by Design, trending of in-process data and analysis of data for product reviews, all pharmaceutical professionals need to ensure that their understanding of an ability to use statistical routines is well developed.

Course Fee £2370.00 plus VAT

Sterile Products Manufacture

Marriott Victoria & Albert Hotel, Manchester, UK
24 - 27 September 2007

One of our most popular courses. A comprehensive, four day course on the latest EU and US GMP requirements for sterile products manufacture, plus practical advice on how to ensure compliance in a cost-effective and scientifically sound way.

Course Fee £2065.00 plus VAT

GMP for Clinical Trials Manufacture and Supply

Marriott Victoria & Albert Hotel, Manchester, UK
1 - 4 October 2007

Essential training in current EU and US GMP regulations for the manufacture, testing, importation and distribution of clinical supplies. As last year, we have invited a European regulatory inspector to give a keynote talk on GMP expectations and current regulatory trends.

Course Fee £2065.00 plus VAT

Good Documentation Practices

Manchester Airport Marriott Hotel, UK
9 -10 October 2007

This course is essential for anyone wishing to make their documentation system more efficient, cost-effective, user-friendly and compliant with EU and US GMP requirements. The course will be highly participative – you will design key documents and perfect your document writing skills.

Course Fee £1195.00 plus VAT

Pharmaceutical Law & Administration

Qualified Person & Professional Development Training
Hilton Hotel, York, UK
15 - 19 October 2007

All the prospective Qualified Person or pharmaceutical professional needs to know about EU, UK and US pharmaceutical legislation and regulatory bodies. This course provides the depth of knowledge and understanding you really need to act in a professional capacity in a highly regulated industry.

Course Fee £2960.00 plus VAT

Good Autoclave Practice

Marriott Victoria & Albert Hotel, Manchester, UK
23 - 25 October 2007

A comprehensive course on the practicalities of autoclave selection, qualification, cycle design and validation, ongoing performance monitoring and management. You will learn current regulatory expectations for steam sterilisation, how to qualify and validate autoclaves effectively, how to troubleshoot problems and best industry practices for monitoring and management of autoclaves.

Course Fee £1580.00 plus VAT

Chemistry and Pharmacy Registration Requirements

Hilton Hotel, York, UK
29 October - 1 November 2007

Run in conjunction with Regulatory Resources Group, this course is designed to provide you with a clear understanding of technical data requirements for EU and US registration submissions and subsequent manufacture.

Course Fee £2065.00 plus VAT

Book online at www.david-begg-associates.com

David Begg associates
The Pharmaceutical Training Experts

Effective Change Control

Marriott Victoria & Albert Hotel, Manchester, UK
30 October - 1 November 2007

The control of planned and unplanned changes is perhaps the greatest challenge facing any pharmaceutical company and its quality management personnel. This highly popular three day course will provide you with practical guidance on how to simplify your change control systems to make them quick and efficient, whilst at the same time ensuring compliance with regulatory expectations

Course Fee £1580.00 plus VAT

Pharmaceutical Packaging GMP Compliance at the Operational Level

NEW VENUE

Clontarf Castle Hotel, Dublin, Ireland
6 - 8 November 2007

Key EU and US GMP requirements for pharmaceutical packing operations, including up to the minute developments in security systems and ISO GMP expectations for primary packaging components.

Course Fee £1820.00

Analysis and Testing

Qualified Person and Professional Development Training

Marriott Hotel, York, UK
12 - 16 November 2007

An intensive course covering the major analytical techniques used in our industry, allowing you to understand why we select certain types of analysis for certain applications and the validation expectations for them. We will also explain current EU and US GMP expectations for the QC laboratory.

Course Fee £2960.00 plus VAT

Qualified Person & Professional Development Training

FREE SEMINAR

Marriott Hotel, York, UK
13 November 2007

Interested in becoming a QP? Why not attend this free seminar to find out more about what we can offer. Learn about what is required to become a QP and see one of our training modules in action.

A-Z of Pharmaceutical Water Systems

Marriott Victoria & Albert Hotel, Manchester, UK
19 - 22 November 2007

This four day course will provide you with up to date information on EU and US regulatory expectations for water systems and practical advice on system design, validation, monitoring and management, as well as troubleshooting and risk assessment. In short, all you will ever need to know about water systems!

Course Fee £2065.00 plus VAT

Pharmaceutical Good Manufacturing Practice

NEW AMSTERDAM COURSE

Amsterdam Marriott Hotel, The Netherlands
3 - 6 December 2007

Europe's most popular GMP course!
Amsterdam course added by popular demand.

Course Fee £2375.00

Pharmaceutical Legislation Update Continuing Professional Development for Qualified Persons and Technical Personnel

CPD

Manchester Airport Marriott Hotel, UK
4 December 2007

Your annual top-up!
Current and proposed changes to EU and US legislation and GMP requirements and their impact on QPs and technical managers.

Course Fee £630.00 plus VAT

Get in touch now to book your place on any of these courses

Call us on +44 (0) 1751 432999 or email: courses@david-begg-associates.com

Industry News

EU News

New Variations Proposal

On 10 July 2007 the Commission issued a draft proposal for a Directive to amend the Variations sections of Directives 2001/82/EC and 2001/83/EC. The objective of the proposed amendment is to modify the legal basis of the variations regulations so that all authorised medicinal products, including those authorised at a purely national level, are subject to the same criteria for the evaluation, approval and administrative handling of changes, regardless of the procedure under which those medicines were initially authorised.

The legal basis of the current variations regulations limits their scope to the following medicinal products:

- medicinal products which have been granted a Community ('centralised') marketing authorisation in accordance with Regulation (EC) No 726/2004;
- medicinal products which have been granted a marketing authorisation in accordance with the mutual recognition and decentralised procedures;
- medicinal products which fall within the scope of application of Directive 87/22/EEC; i.e. biotechnology and other 'high-tech' products.

Thus, they do not currently apply to changes to marketing authorisations for medicinal products granted at a national level by a Member State competent authority (referred to as "purely national" marketing authorisations). In the absence of Community harmonisation, national rules vary from one country to the other, leading to disharmonised requirements and an unnecessary administrative burden.

The proposed amendments will thus bring much needed consistency to the variation process, which will benefit pharmaceutical companies, the regulators and, ultimately, patients throughout the European Union.

Comments on the proposals should be sent to the European Commission before 21 September 2007.

This and other "hot topics" will be discussed at our one day "Pharmaceutical Legislation Update" course to be held at the Manchester Airport Marriott Hotel on Tuesday 4th December 2007.

Draft Revision of Annex 6, Medicinal Gases

A revised version of Annex 6, Manufacture of Medicinal Gases, was issued as a draft for comment on 31 July 2007.

One of the major drivers for this revision is the need to define more clearly what constitutes a starting material when dealing with medicinal gases and what is a bulk medicinal product. The draft includes a general rule to encourage a harmonised approach to this distinction across the EU.

Other changes include more detail on:

- requirements for storage of cylinders and mobile cryogenic vessels,
- the conduct of risk management on tankers used to transport medicinal gases
- other measures to address cross-contamination concerns.

The deadline for comments to be sent to the EMEA is 31 December 2007.

Proposed Revisions to Annex 1?

We hear from sources close to the regulatory authorities that a revised version of Annex 1, Manufacture of Sterile Medicinal Products, is close to release as a draft for comment.

Manufacturers will be delighted to hear that our sources tell us that the current requirements for 5 micron particles in Grade A zones and Grade B areas at rest will be revised to bring them more in line with the requirements of International Standard ISO 14644-1 for ISO 5 zones (29 particles per cubic metre).

Additionally, we hear that the new draft will draw a distinction between sample volume requirements for classification and for monitoring, as proposed in the previous draft of September 2005.

We stress that, in the absence of actual published proposals, this is currently just hearsay. However, watch this space!

Proposed changes to GMP regulations for sterile products will be covered during our 4 day "sterile Products Manufacture" course to be held at the Manchester Victoria & Albert Hotel from 24 to 27 September 2007 and during our "EU GMP Requirements for the Manufacture of Sterile Products" courses to be held in the USA in spring 2008.

US News

USP Revision of General Notices

The United States Pharmacopoeia (USP) is proposing to revise the General Notices of the USP-NF. This proposed revision attempts to clarify the distinction between "official" (legally enforceable) and "authorised" (informational) text.

Currently, all General Chapters are official by virtue of their inclusion in the USP-NF, which are recognised in law as official compendia of the United States. USP-NF currently distinguishes between enforceable and informational General Chapters by means of chapter numbers: Chapters numbered below 1000 are intended to be enforceable by FDA or other regulatory authorities while chapters numbered above 1000 are intended to be informational only.

USP say that they are aware that this numerical distinction is not entirely adequate and may cause confusion within industry and regulatory authorities. Inclusion of General Information Chapters in the official compendium may at times cause them to be given more regulatory status than USP intended. In addition, the distinction is imperfect as some chapters with numbers over 1000 may be referenced in a monograph, which makes them mandatory for those monographs.

This draft revision of the General Notices proposes clarifying the text that is official in a new way:

- All USP-NF monographs would be official.
- The General Notices would remain official.
- All General Chapters in the USP-NF would be official whether the chapter number is above or below 1000. These would include every General Chapter that is referenced in an official USP-NF monograph. Other General Chapters also would be included, such as those that provide information that is necessary to performing compendial procedures or to assuring product quality, and those that are anticipated to be referenced in a monograph in the near future.
- Information currently published in the USP-NF, but intended to be informational, would move to a new volume (the "Companion Volume") that would not be called USP-NF in order to clarify to regulatory authorities that these materials are not intended to be enforceable. Some of the USP General Chapters would move to the Companion Volume and would retain their original chapter numbers. The Reference Tables section of the USP, including the Description and Solubility table, also would move to the proposed Companion Volume as authorised text.
- Pending Standards would remain authorised text.
- Other text, such as Information monographs, would remain authorised and would remain outside of the USP-NF.

In addition to the changes proposed to clarify the distinction between "official" and "authorised" text as described above, other changes are proposed to alter the status of some USP Chapters from "informational only" to "enforceable by FDA or other regulatory agencies." Chapter <1231> Water for Pharmaceutical Purposes is one of the informational chapters that could be elevated to legally enforceable status.

Coming to America

After 22 years of offering training courses to the pharmaceutical industry in Europe, we have taken the decision to run a series of residential training courses in the USA.

The first courses we will be offering capitalise on our extensive knowledge of the pharmaceutical regulatory scene in Europe and are designed to help those companies in North America who are currently providing commercial product or clinical supplies to the EU, or are considering doing so in the near future.

Thus our first two training courses in the US will be...

- European Pharmaceutical Legislation and the Role of the Qualified Person
- EU GMP Requirements for the Manufacture of Sterile Products

We have chosen these two topics because we have found from our extensive consultancy and GMP audits in North America that these issues are poorly understood by American companies and so regularly lead to observations and criticisms during European regulatory inspections.

Our first courses will be held during the first quarter of 2008 and so we decided to choose venues which will provide a little warmth and sunshine – San Diego, California and San Juan, Puerto Rico.

We are really excited about this new venture and we are all looking forward to growing our presence in North America to match that in Europe. If you have colleagues in the US who you think will benefit from attending these courses, please email them to look out for our advertising. The courses will be promoted soon, both by mail and via our website.

Our Initial Programme of Courses in America

European Pharmaceutical Legislation and the Role of the Qualified Person

26-28 February 2008	San Juan Marriott Resort, San Juan, Puerto Rico
15-17 April 2008	Marriott San Diego Hotel and Marina, San Diego, California

EU GMP Requirements for the Manufacture of Sterile Products

1-3 April 2008	San Juan Marriott Resort, San Juan, Puerto Rico
27-29 May 2008	Marriott San Diego Hotel and Marina, San Diego, California










Location, Location, Location…

The Manchester Airport Marriott Hotel

We searched long and hard to find a hotel for short courses that is convenient for air, road and rail links, so that our delegates from all over Europe can get to the venue quickly and easily.

We believe we have the ideal location in the Manchester Airport Marriott Hotel. For us it ticks all the boxes…

- ☑ Conveniently located at a major international airport, but not on the tarmac!
- ☑ Free shuttle bus to and from the airport's three terminals
- ☑ Situated on a junction of a convenient motorway (M56) with extensive parking facilities
- ☑ Close to a railway station (Manchester Airport) and well served by taxis and shuttle buses
- ☑ Top quality accommodation, specially adapted for business travellers - as one would expect from a Marriott Hotel
- ☑ Excellent swimming pool, fitness and leisure facilities
- ☑ Good dining in the "Players" restaurant
- ☑ Less than 30 minutes by taxi from Manchester city centre

Oh, and the conference facilities are really good too!

For short courses, the Manchester Airport Marriott has everything you (and we) could possibly need.

So why not come along to one of our short courses here – you won't be disappointed.

We shall be running the following courses at the Manchester Airport Marriott Hotel during the second part of 2007 and early 2008…

Pharmaceutical Legislation Update
4 December 2007

Essential Elements of Good Control Laboratory Practice
5 February 2008

Investigating Out of Specification Results
6 February 2008

Ongoing Stability Testing
7 February 2008

Cleaning Validation
26 & 27 February 2008

DBA People

A Passion for Wildlife

How a boyhood interest was rekindled for Bob Pietrowski.

Bob has been interested in nature and wildlife all his life. As a schoolboy he was a keen birdwatcher and spent his school holidays in the nearby woods and streams, observing all manner of animals and plants at close quarters.

Over the years Bob's interest in nature and wildlife receded as university life, work and eventually family took over. Then, a few years ago Bob and his wife, Christine, decided to celebrate freedom from the children by visiting the Kruger National Park in South Africa.

"For me it was an amazing experience and it re-awakened an old passion for animals" says Bob. "Since then, my spare time has been largely devoted to planning more wildlife holidays and purchasing photographic equipment to record our visits".

The South African trip was followed by a safari in Kenya's Masai Mara Reserve.

"Absolutely overwhelming for the numbers and diversity of animals, and to see the lions of the Marsh Pride – stars of the "Big Cat Diary" TV series – was a real privilege".

Last year Bob realised a lifelong ambition to visit the Galapagos Islands.

"I brought a new telephoto lens for the trip, but wasted my money – the animals are so fearless you can walk right up to them! Most of my photographs were taken from within 2 metres".

"As for the future, I have two major objectives; to see the great apes in the wild and to improve my photographic skills so that I can do those magnificent animals justice".

A few of Bob's photographs from recent trips are shown here.

In the next DBA Journal

Industry News: as ever, we search for regulatory changes so you don't have to, Tech Talk: air filters for tablet manufacture – getting the balance right! Location, Location, Location…: Kirkbymoorside – home of DBA, DBA People: Mike Halliday, Forthcoming Courses: a review of our training courses for early 2008.

If you have any comments or suggestions for the next issue of the Journal, please email us at journal@david-begg-associates.com

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