

news



Chairman's Review

I feel guilty (well, almost!) writing this short review with a view of the sun drenched vineyards of the Marlborough district of New Zealand and the Cloudy Bay Mountains as a backdrop to complete the picture. My mind, microbiologically speaking, is rather narrowly focussed at present. The lure of the winerys in this area present an unrivalled opportunity for sampling some of the worlds best wines, most notably the Sauvignon Blancs with Chardonnays and Pinot Noirs coming close behind.



As you may read elsewhere the new Committee held its first meeting on January 23rd in Northampton. I feel very positive about the way in which the new Committee (well some new, plus some old) is beginning to gel and work together as a team with excellent agreement upon the allocation of tasks to be undertaken in securing a variety of events for 2002 and beyond. The keyword to our programme is consolidation with a strong emphasis on better, wider and more timely publicity. In addition, we will make every attempt to move in a controlled manner to increase the Membership and profile of PharMIG. I am constantly amazed that there are still pharmaceutical companies, and people in those companies, who remain unaware of PharMIG's activities. So, may I leave you with one very clear message – please make every attempt to spread the word about PharMIG and encourage many more Members. In helping this aim, don't forget our leaflet "Essential Facts and Information about PharMIG". More copies available from the PharMIG office.

Looking forward to meeting as many Members as possible during 2002.

David I R Begg
Chairman, PharMIG

In news issue 8

Action Group Update	Page 2
Editors Note	Page 3
Bacterial Endotoxin Action Group	Page 4
Training on Cleaning and Disinfection	Page 13
PharMIG Conference 2002	Page 14
Sterility Testing	Page 15
Diary Dates	Page 16



Members of the Steam Sterilisation Action Group

PharMIG Action Group

The year 2002 has begun and the Action Groups have not ceased in momentum. I am pleased to introduce myself Natasha Gibbs as the new Action Group Co-ordinator. My aim is to ensure that the current Action Groups continue to provide a service to the Pharmaceutical industry.

We currently have four active Action Groups. The Steam Sterilisation Action Group has a new leader Joseph Day who now has the task of driving the Group and ensuring that their monograph is issued in a timely manner. Expect to see lots of things happening this year with this Group.

The Bacterial Endotoxin Group leader Lynne has been frantically collating the data from their questionnaire, which she presented at the PharMIG Conference last year. This is available in this issue of Pharmig News. The group will then be working on incorporating this information into their monograph.

Trudy and her team on the Disinfectant Action Group have been working hard on their sections for their monograph, which at this stage looks quite impressive.

The Non-Sterile monitoring Group reformed last year they have now prepared a comprehensive questionnaire, which should be reaching you after Easter. I would like to take this opportunity to ask that PharMIG Members continue to support the Action Groups by responding to questionnaires, without your input we cannot form an industry influenced guideline.

I would like to thank the Action Groups for their continued enthusiasm and drive, but most of all I would like to thank you the reader for all of your input. Without you the Action Groups would not, exist I therefore ask for your continued support.

Natasha Gibbs
GlaxoSmithKline, Ware

Patsy Petri-dish

Dear Patsy Petri-dish.

The chemists who work along the corridor from our lab always seem to get lots of money for expensive equipment. How can I get some of this money for us?

Impoverished from Slough

Dear impoverished,

I understand your feelings and microbiology methods have traditionally been less expensive than chemical ones. I feel that this is now changing and many companies are looking at the value of tests rather than the cost. This is especially true of companies trying to achieve minimal inventory levels.

I tend to find that chemists are also good at justifying why they want the money. Try and concentrate on what savings you can make. Think about whether your results hold up the release of the batch, will the new equipment you desire save technician time, will it allow you to be 21 CFR Part 11 compliant, has it ever been mentioned by an auditor, will it save engineering time to have more reliable equipment (just think of autoclaves)

Don't sell yourself short, if your first argument doesn't work try another one. Try borrowing a justification written by a chemist and nick some of their ideas. Above all remain positive and don't be put off,

Yours sincerely

Patsy

DEAR PATSY,

I KNOW THIS IS A DAFT QUESTION BUT I'M FINDING THAT THE NEW PETRI-DISHES WE HAVE IN THE LAB ARE MORE DIFFICULT TO STACK THAN THE ONES WE USED TO HAVE. THEY SEEM TO WOBBLE WHEN PILED UP, CAN YOU HELP? YOURS CLUMSY FROM CLEVELAND

Dear clumsy from Cleveland,

check that your new Petri-dishes are triple vented and that they have not been changed to single vented. I would also recommend increasing stack stability by only stacking a maximum of 10 plates in a pile.

If others are also having this problem, I suggest you phoning the supplier and asking their advice. I have always found them most helpful in such situations, they will not find it a daft problem as it's their business to keep their customers happy.

Good luck,

Patsy

Please send in any questions to Patsy to the Pharmig office or use the telephone, fax, email or web - please!



editors note

Dear reader, You may have noticed that there are some changes on the PharMIG web page. We are introducing password protection so that some parts of the web page will only be accessible to PharMIG Members (remember one person joining from your site makes you all Members). We wish to have a balance between providing information to everyone free but also recognising that we do not want to give valuable information to people that have not paid a Membership fee. The passwords will be given when this year's subscription has been paid. An example of our approach is that all the newsletters will be on the web page but for the most recent 2 years non-members will only have access to the front page to give them a taste of what they are missing!

We live in a changing world and we must move with the changes but are all of them for the best? The EP 4.02 now states that for WFI, Purified and Highly Purified Water we should use media S, which is R2A. I know that if you use R2A for poor quality water or potable water you can achieve something like a 10-fold increase in the number of CFU detected. You then have to cut the amount you filter by a factor of ten so that you can maintain a countable number and you may have to justify changing your limits. The water you are using to make your products or WFI etc. is no better than it was before. It therefore does not improve the quality of your products. Good controlled WFI systems do not give an increase in count with R2A because nothing is there (or is there - see Paul Newby's article on Non culturable in the next issue of PharMIG News). If you have a problem with your water system it may show it up earlier if you incubate your plates for long enough. Because it's a minimal media which should be incubated at a low temperature it will take longer for the colonies to grow. Validating your test is an interesting challenge! Do you use your nice healthy lab cultures as normal, or stress them or use wild types only found by the R2A? Of course there is a possibility that you may find that your water system is no longer able to meet regulatory requirements then life really will get interesting! It all looks very much like a driver to introduce rapid methods, quick results with sensitivity.

Paul Lovegrove-Saville

PharMIG

Bacterial Endotoxin Action Group

By Lynne Arnot
Tepnel Scientific Services

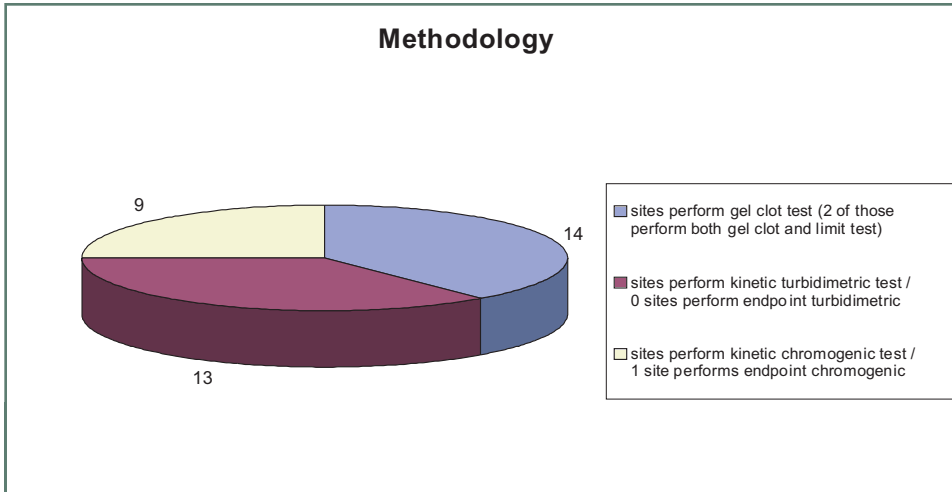
In August 2001, the Bacterial Endotoxin Action Group issued its first questionnaire. The questionnaire was broad based, covering a variety of endotoxin related topics. No single topic was examined in great detail as the aim was to benchmark current practice within the pharmaceutical industry. Whilst the Group felt that the new, harmonised tests are greatly improved, we felt there was still ambiguity over some areas. It was hoped that the questionnaire responses would highlight discrepancies and (hopefully!) consistencies within testing throughout the industry.

103 questionnaires were sent out and 30 were returned of which 6 were not relevant to site. The current Action Group met in October 2001 to collate the questionnaire responses. Those of you who attended last year's Conference may remember I was able to give a brief update during the Action Group review section (it was day one, so chances are one or two of you may remember?!). As promised at the Conference, the findings of the 24 completed questionnaires are summarised here.

1. Methodology

The first section dealt in very general terms with all aspects of methodology. We were interested to see what methodologies are currently in use throughout the industry, how many sites routinely use

more than one method, what standard ranges etc. are run and what lysate suppliers are used.



The breakdown of methodology used is depicted in figure 1.1.

Figure 1.1

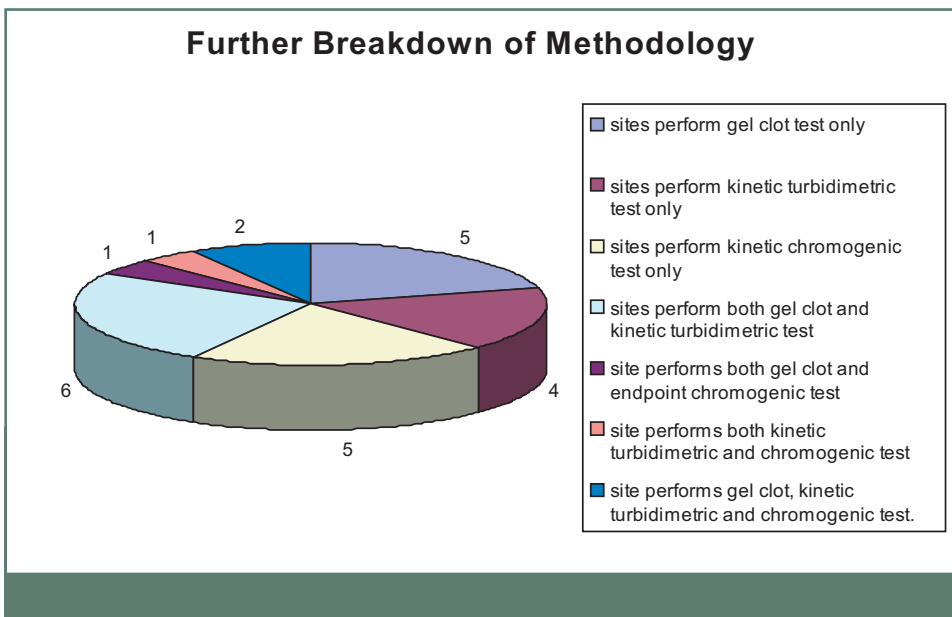


Figure 1.2 shows a further breakdown into how many sites perform one, two or all three methodologies.

12 sites indicated that they have tested the same sample by different methods. Of these, 7 stated that the results always correlated well and 4 stated that the results sometimes correlated well. It is perhaps slightly worrying that one third of those who test by more than one method are only getting results to correlate well sometimes, although I'm sure the positive thinkers amongst us will be glad to see no-one opted for the response of "rarely" correlates well! Of course, the more negative thinking or cynical amongst us (surely no pharmaceutical microbiologists?!) may suspect that the site who didn't indicate one way or the other may have been too afraid to face the truth! We may never know!

We asked how many sites run standard series with every assay. 20 sites indicated that they do, whilst 4 do not. The numbers of standards run is given in figure 1.3. The Group believe that the sites who have responded that 2 standards are routinely run have misinterpreted the question as referring to numbers of replicates, since a three standard curve is a minimum requirement. The majority of sites are running 4 standards for all methods, with some of the kinetic methods varying depending on how many samples are being assayed.

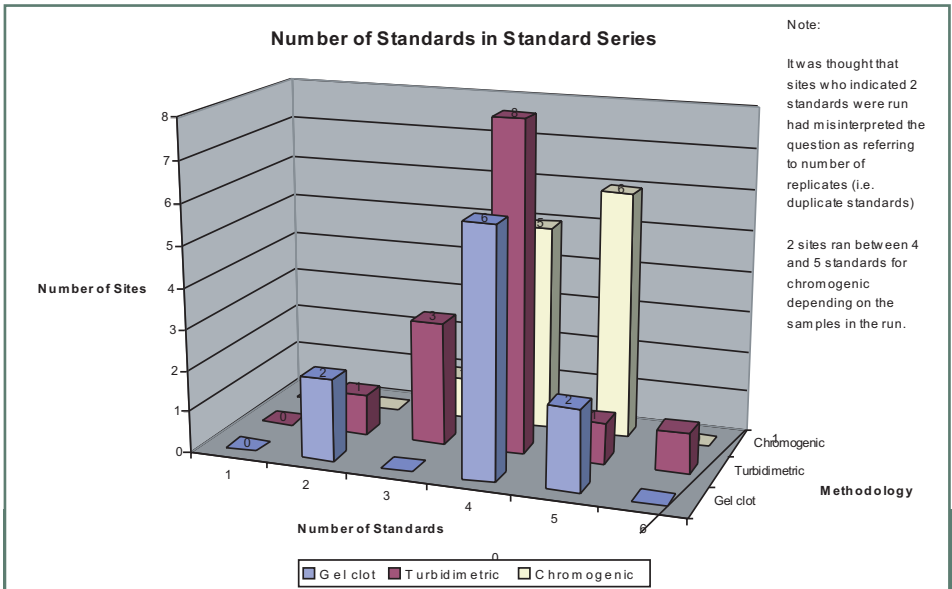


Figure 1.3

The standard ranges run are depicted in figures 1.4 to 1.6 for gel clot, turbidimetric and chromogenic respectively. We realised with hindsight that the question lacked clarity with regard to gel clot methodology as some sites responded "2λ to 0.25λ",

whereas others specified actual EU or IU /ml values. Looking at the graph of standards used for gel clot, it is thought that most equate to 2λ to 0.25λ.

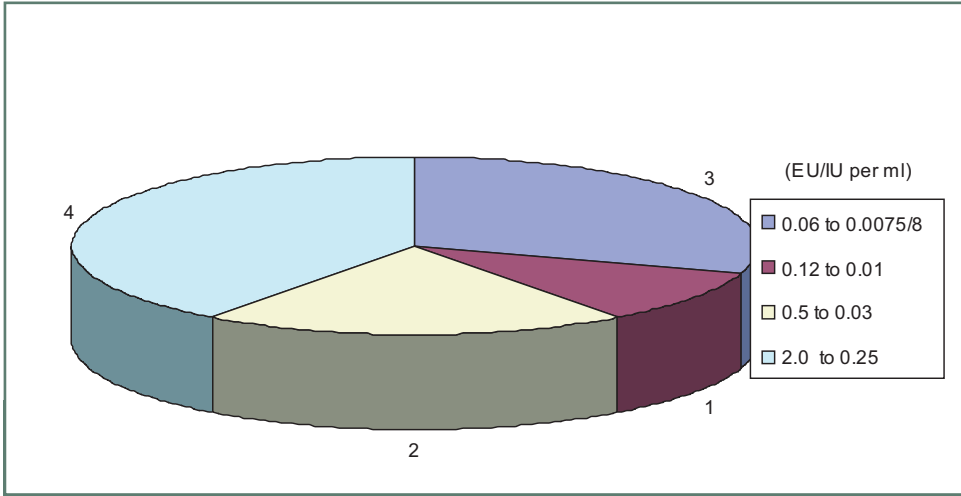


Figure 1.4

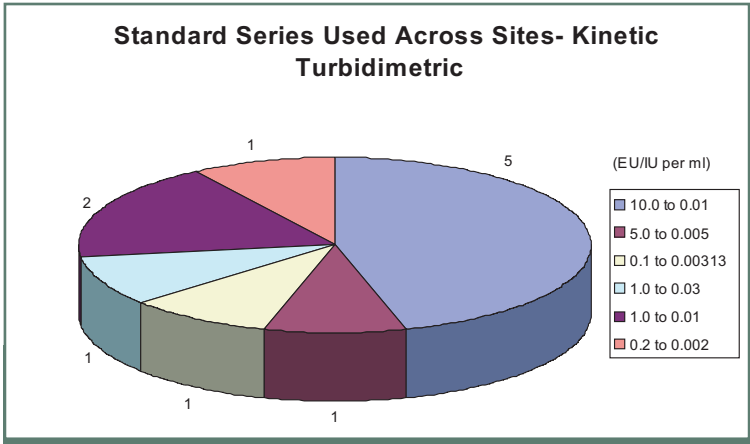


Figure 1.5

Standard Series Used Across Sites- Kinetic Chromogenic

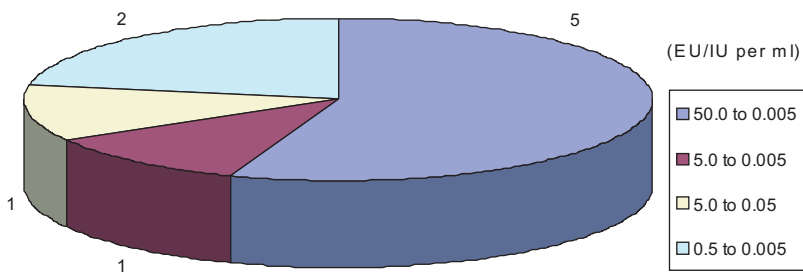


Figure 1.6

2 sites run standards and blanks at the start and end of a run and both said they run a limited standard series. One of these sites indicated that this was dependant on the number of samples in a run, although no cut off number was indicated.

Last but not least in the Methodology section, we asked which lysate supplier (s) you routinely use. This is shown in figure 1.7. We were initially a little concerned about the site who responded "Not Applicable" but my sources tell me that there might be someone out there who does actually prepare their own lysate, so apologies for our initial giggles at this response!

Lysate Suppliers Usage

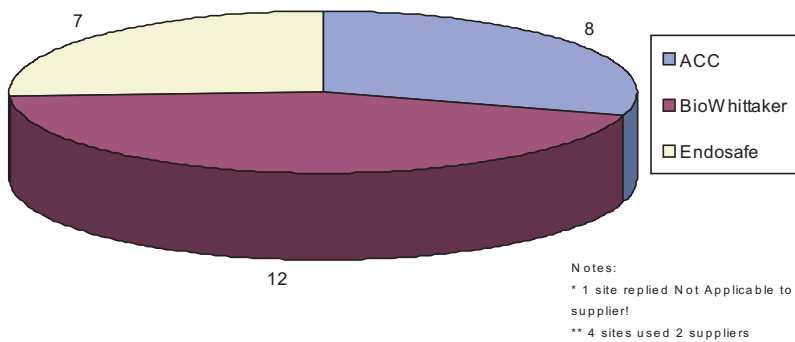


Figure 1.7



2. Sampling

In the second section of the questionnaire, we asked about sampling regimes. Tables 2.1, 2.2, 2.3 show the responses to these questions.

Routinely test from start/middle/end of batches

Yes	12
No	9
N/A	2*

*1 was a water testing site.

1 site had shown comparison between start/middle/end and composite samples.

Table 2.1

Individual versus pooled samples

Individual	18
Pooled	7

2 sites test both individual and pooled although predominantly individual

Table 2.2

Documented storage regime

Yes	13
No	10

Most common storage temperature was refrigeration.

Table 2.3

Of those who had a documented storage regime for waters and in-process samples, we asked for specific details and whether or not such regimes were validated. The most common storage temperature (10 sites) was refrigeration (variously reported as "fridge", "0 to 8°C", "4 to 6°C" or "2 to 8°C") for waters and product dilutions. Storage time under refrigeration varied from 6 hours (1 site), 24 hours (3 sites), 4 days (1 site) and 5 days (1 site). 2 sites used freezer temperature (-20°C) to store waters beyond 6 to 24 hours and 1 site used room temperature to store finished products.

Sites who stated storage times without temperatures used 24 hours (3 sites), 6 hours to 7 days (1 site) and 5 days (1 site).

Of the stated storage regimes, 6 were validated and 5 were not.

The validated regimes were :

- 2-8°C for 4 days
- 2-8°C for 5 days
- 4-6°C for ≤1 day
- 2-8°C C for ≤ 24H
- 0-8°C (no time given)
- 2 – 8°C (no time given)

3. Consumables

In section 3, we asked about consumables used, in terms of whether or not they were certified or tested in-house (see figures 3.1 to 3.4).

There was a slight confusion in the numbers of responses to these questions. It was thought that some responses relating to what consumables are tested for were based on supplier's Certificates of Analysis as well as in-house testing.



Figure 3.1

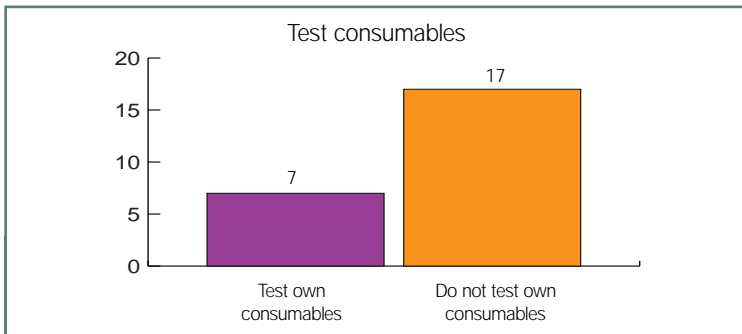


Figure 3.2

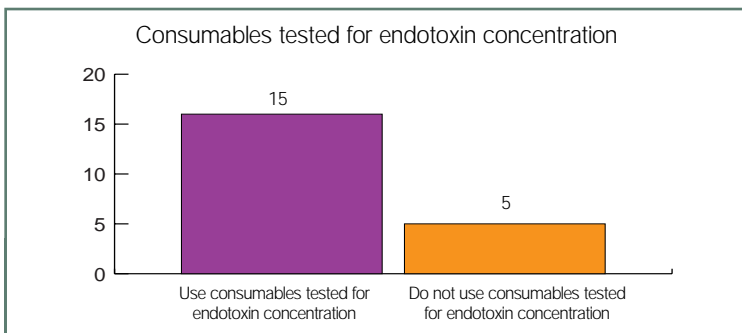


Figure 3.3



Figure 3.4

4. Depyrogenation

Section 4 touched briefly on depyrogenation. See figures 4.1 and 4.2.

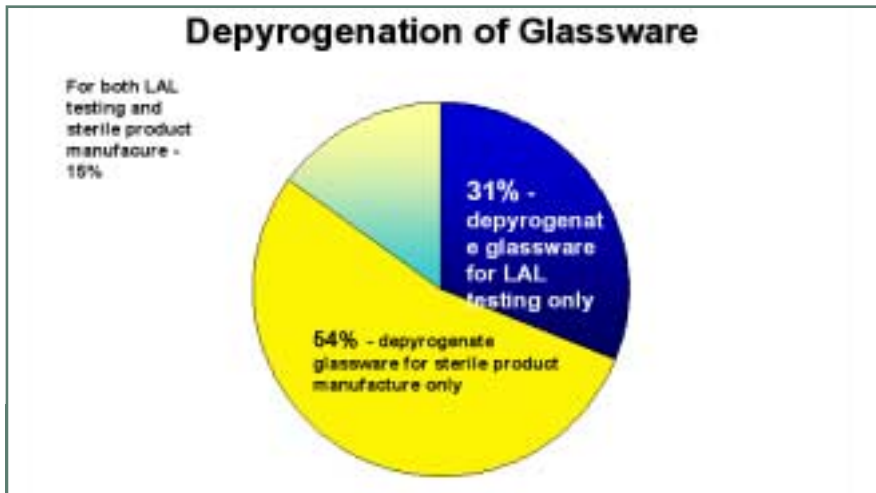


Figure 4.1

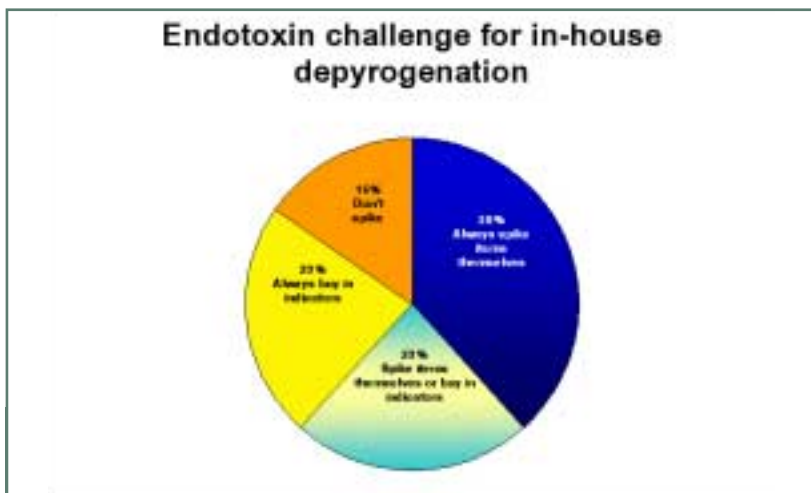


Figure 4.2

More than half of the sites in the survey are not involved with depyrogenation. Of those who are, a variety of spike levels exist but all 8 sites who indicated acceptance criteria use a 3 log reduction limit.

Size of endotoxin challenge ranged from 40 EU/ml (1 site), 3.75 ug (1 site), 1000 EU/vial (3 sites), > 1000 EU/vial (1 site), 1500 EU (1 site), > 5000 EU/ml (1 site), 0.25 – 10,000 EU (1 site), 17,000 EU (1 site) and 25,000 IU (1 site).



5. Problem Products

Section 5 dealt briefly with the testing of raw materials and excipients which may be insoluble and may or may not have set limits.

The methods used to treat problem (e.g. insoluble) products are summarised in figure 5.1.

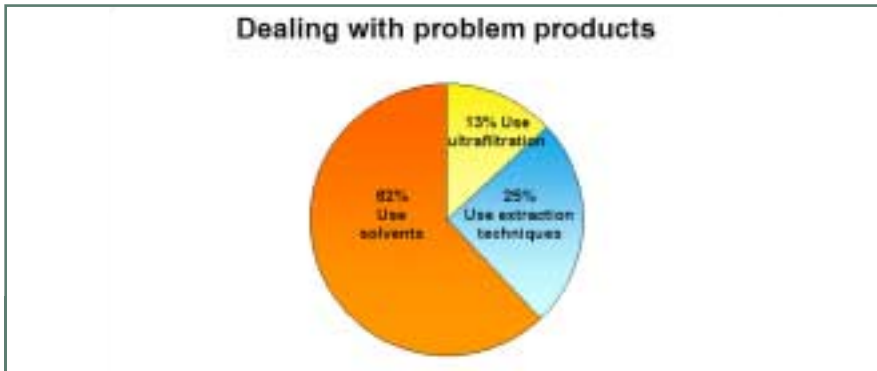


Figure 5.1

9 sites are frequently involved in validating products that have no specified limits.

6 sites routinely test excipients. Only two of these sites test all excipients, one specifying only if used in IV preparations. Of those sites that test excipients, 3 base their approach to setting limits on the contribution the material makes to the final product.

13 sites routinely test raw materials for endotoxin.

6. Calculations

In section 6 we asked about the calculations used in endotoxin testing.

The number of decimal places routinely reported to varied from 1 to 4 as shown in table 6.1.

Number of decimal places	Number of sites
1	1
2	11
3	6
4	2

Table 6.1

1 site stated that this depended on software and sample specification.
 10 sites use a rounded figure for gel clot MVD calculations, 3 do not.
 12 sites use only linear regression to calculate results for kinetic methods, 9 do not.
 1 site uses Linear Regression and Powercurve for validation, and Powercurve for routine testing.

18 sites use statistical methods for measuring replicate accuracy in kinetic methods, 3 do not.
 Of those that do, % co-efficient of variation (%cv) is used for 16 sites.
 Limits for replicate accuracy varied between 10 and 25 % as shown in table 6.2:

Number of decimal places	Number of sites
1	1
2	11
3	6
4	2

Table 6.2

Congratulations, by the way, to those of you who spotted the "deliberate" error in questionnaire – no question 6b!! Just keeping you on your toes!

7. pH

The number of sites that perform pH measurements during endotoxin testing is given in table 7.1.

pH	Yes	No
Validation	20	3
Routine Testing	8	16
Sample only	12	11
Sample + lysate mix	14	10

Table 7.1
Some of the sites that do not measure pH were water testing sites.

8. Harmonisation Issues

We asked for your views on harmonisation issues. Whilst most of us would agree that the recently harmonised texts in the USP and Ph. Eur. are a vast improvement (recognition of kinetic methods in USP and loss of the dreaded λm and $\lambda m'$ from the Ph. Eur.!), we felt that some specific points may have been overlooked.

11 sites felt that omission of Minimum Valid Concentration (MVC) calculation from USP test was a problem, 7 did not. 14 sites felt that omission of use of Control Standard Endotoxin (CSE) from USP test was a problem, 4 did not. 8 sites felt that omission of Maximum Valid Dilution (MVD) calculation based on dosage per m² body surface area from Ph. Eur. test was a problem, 11 did not.

With a view to using the information gathered from this questionnaire to publish a set of guidelines for bacterial endotoxin testing, last but not least we asked for any other comments and /or issues you would like to see covered by such a publication. They included the following:

Conclusion

It would appear (reassuringly!) that for general routine testing we are adopting fairly standard practices for some aspects (numbers of standards tested, ranges used etc.) but that areas surrounding the wider context of the test are somewhat greyer (validation issues, sampling, depyrogenation protocols etc.). It is the intention of the Bacterial Endotoxin Action Group to publish some form of technical monograph. In order to do this, your views are always needed. If you feel that we have missed anything out or need to expand on any particular section, please let us know. Some of the sections within this questionnaire could warrant whole questionnaires of their own, so please let us know if there is any you would like more information on.

Endotoxin recovery from depyrogenation of rubber closures

Bulk product testing

Calculations for solid and liquid formulations

Validation guide for solid / liquid dosage forms

Regulatory / training requirements (IQ assays, technician proficiency etc.)

Sampling guidelines

Problem products / insoluble products

List of known inhibitory solvents and their inhibitory concentrations

Validation requirements for alternative lysate suppliers

Industry views on hot spiking versus dilution spiking methods

Variable PPC levels for bulk products containing high endotoxin levels

Definitive answer on use of Polynomial versus Linear Regression

Guidance on use of consumables / plastics / storage of samples etc.

All that remains to say for now is many thanks to all my comrades in the Group (and one or two of our respective husbands!) for their help in collating and presenting this data (I still owe you all drinks, I know!) and most of all thanks to all those of you who took time out of your busy days to complete the questionnaires and give us positive feedback.

Lynne Arnot

On behalf of PharMIG Endotoxin Action Group:

Tim Sandle (BioProducts Laboratory)

Angela Fuller (Sanofi-Synthelabo)

Michelle Cullen (Pfizer)

Alan Hoffmeister (Charles River Endosafe)

Practical Training on Cleaning and Disinfection

Wednesday 10th & Thursday 11th April 2002 at
The University of Bath
Claverton Down,
Bath BA2 7AY

For the second year running, we are holding a training course on Cleaning and Disinfection at the University of Bath. I am pleased to say that it has proved very popular again and there are just a few places left for those who still wish to register. Further details are outlined below.

Introduction

Cleaning and disinfection of premises and equipment play a significant part in contamination control of any pharmaceutical manufacturing process. A detailed understanding of the principles behind cleaning and disinfection is required if a successful sanitization strategy is to be implemented. This course has been designed not only to provide an overview of the key microbiological issues involved in cleaning and disinfection, but also to demonstrate how that knowledge is applied in practice.

The course will be of benefit to scientists involved in microbiological contamination control, to newly recruited auditors, to those involved in the management of cleaning and disinfection and to production supervisors and operators. Attendance will be limited to 40 to facilitate discussion and practical demonstrations. A certificate of attendance will be issued for training records.

Course fees

Course fees are detailed below and include all meals, refreshments and course documentation. For anyone wishing to arrive on the evening of Tuesday 9th April, bed and breakfast is available at an additional cost.

Cheques should be made payable to PharMIG and crossed A/C Payee only. Fees are exempt of VAT.

Member Fees £685.00 per delegate
Non Member Fees £770.00 per delegate
Arrival on 9th April £55.00 per delegate
Dinner on 9th April £25.00 per delegate

Registration process

Simply complete a registration form and return directly to the PharMIG Company Secretary with your payment or fax ahead your registration details to 01920 871156. Places are limited and reserved on a 'first come, first served' basis, so book early to avoid disappointment. All places will be held provisionally until full payment is received. Confirmation of an allocated space will be sent by post with travel directions

Speakers & Facilitators

Dr Rosamund Baird: Honorary Member, PharMIG

Mrs Rachel Blount: Business Manager, DiverseyLever

Miss Christina Bradley: Manager, Infection Control Research Laboratory
City Hospital, Birmingham

Dr Ansley Crockford: Operations Manager, Validation Services
Bovis Lend Lease Pharmaceutical

Dr Annette Ellison: QC Microbiology Manager, Boots Contract Manufacturing

Dr Robert Johnson: Director of Quality International Antibiotic Supply,
GlaxoSmithKline

Mr Andy Martin: QA Microbiology Manager, Chauvin Pharmaceuticals Ltd

Mr Brian Midcalf: Consultant, School of Continuing Education, Leeds University

Mrs Kim Morwood: Technical Director, MGS Laboratory Ltd

Dr Anthony Smith: Senior Lecturer, University of Bath

Programme Wednesday 10th April

9.30 - 10:00 Tea/Coffee and Registration

Disinfection Theory: A question of semantics, Disinfectants types and modes of activity, Factors affecting activity, Mechanisms of resistance

Hot Topics: viruses, prions and biofilms

Disinfection in Practice - Isolators: Gassing systems, Cycle development, performance qualification, and biological indicators, Operating control factors, Surface decontamination, Directives and guidelines

LUNCH BREAK

Disinfection in Practice - Sterile and Non-sterile Facilities: Cleaning techniques, Selection of agents, preparation, filtering, storage and dilution, Compatibility and rotation of solutions, CIP, Residues, SOP's, records, documentation

Microbiological Aspects of Disinfectant Validation: Historical background, Phases of CEN tests, Suspension, surface and sporicidal tests, Practical considerations

TEA/COFFEE BREAK

Practical Demonstration and Laboratory Work: Hand washing techniques and validation, Disinfectant and detergent concentration testing, Demonstration of environmental contaminants, Filtering of disinfectants

DRINKS AND DINNER IN WESSEX HOUSE

Programme Wednesday 10th April

Disinfection Challenges of Water Systems: Hygienic design, Problematic micro-organisms, Cleaning and disinfection methods

Biofilm: prevention and removal

TEA/COFFEE BREAK

Role of Environmental Monitoring in Contamination Control: Development of a monitoring programme, Monitoring methods: traditional vs. rapid, Microbiological standards: sterile vs. non-sterile, Discussion of environmental monitoring results from previous day

Case Studies: Small working groups to discuss cleaning related issues and report back on a suitable course of action

LUNCH BREAK

Validation: Regulatory guidelines, Methods of detection of detergent and disinfectant residues, Acceptance criteria

Interactive Audit Workshop: Testing audit skills relating to cleaning and disinfection issues, Final Discussion, Close of session, A fully scheduled programme will be issued to all participants closer to the time.



PharMIG Conference 2002

The PharMIG Conference and AGM for 2002 has been scheduled for Wednesday 27th and Thursday 28th November 2002. By popular agreement, the venue will again be the Moat House Hotel in Peterborough.

The Conference Sub-committee have held two meetings this year to hotly debate the two day programme!

The theme this year will be:

Quality Challenges in Pharmaceutical Microbiology

A great selection of presentations is being put together and includes:

- Current Challenges in Pharmaceutical Microbiological QA
- Environmental Contamination Control
- Risk Assessment – Microbiological Issues
- Microbial Failure Investigations Simplified!
- Engineering Microbial Quality into Existing Facilities
- Challenging your Microbial Training Programme

There will of course be a selection of commercial companies present in the exhibition suite and this year looks to be the biggest and best yet judging by the interest shown for exhibition space!

Round Table Sessions

Wednesday 27th November

A set of round tables will be available during lunch for informal discussions on the following topics:

The Disinfectant Action Group

The Bacterial Endotoxin Action Group

The Steam Sterilisation Action Group

Open Discussion Sessions

Thursday 28th November

These very popular sessions will include:

Session 1 Current Practices in Pyrogen Testing

Session 2 Validation Issues – are there any?!

Session 3 Microbial Quality in Non-sterile Manufacturing

Sterility Testing

by Sharon Johnson
Baxter Healthcare Ltd

"Why perform the sterility test?" – is a question often asked. It remains a fact that a sterility test remains a requirement for the release of sterile medicinal products, unless Parametric Release is approved by the competent authority. This presentation will discuss the test, the proposed harmonised test presented in Pharmeuropa April 2000, and the future.

Before looking at the test method itself it is important to understand the limitations of the test, and its value. As for any finished product test only a sample of the batch is taken to perform the sterility test. The probability of selecting a contaminated unit is statistically low and is a well documented fact. With this fact in mind what assurance does a sterility test showing negative growth give you with respect to the sterility assurance of the process.

However, for aseptic processing there has been a move over the last 5 years, or more, to directed sampling. In this respect the samples are taken during times of risk during batch manufacture – after aseptic set-up and manipulations, intervention etc... Indeed the EP 2000 recommends this practice. In this instance the sterility test result may give you useful feedback about the robustness of your aseptic process.

When looking at the sterility test method employed by worldwide pharmacopeia it has not changed significantly over time – certainly in the 20 years I have worked in the Pharmaceutical industry. Simplistically the test involves taking a number of individual test units, then either filtering the contents through a membrane filter, adding the filter to liquid medium (or adding the liquid medium to filter), or directly inoculating the sample into liquid medium. The method describes the number of samples to be taken, how much volume from each test unit should be tested, the incubation conditions, how to validate the test with your product, and how to interpret your result.

As already mentioned very little has changed, or obviously changed, over time with the one well known exception being the incubation period which was increased from 7 days to 14 days – this because experience from the field was that sterility tests failed after more than 7 days incubation. From first hand this is a statement of fact – sterility tests have shown positive growth after 11 or 12 days incubation.

While the Pharmacopeia has not changed significantly the regulatory expectations with respect to the sterility test have increased along with improving GMP and manufacturing standards. It is perhaps reasonable to extrapolate the conditions for manufacture to the test environment particularly when positive contamination of the test is frequently considered to be due to the test environment and / or technician. The concern here is that a test might, too easily, be considered to be invalid due to the test environment without due consideration to the possibility of the result being a true indicator of product quality. The Pharmacopoeia states that a retest can be conducted under certain conditions – one being that the first result is conclusively shown to be invalid. What assurance does a satisfactory retest give you?

How would you conclusively invalidate your positive sterility test – there is now talk that contaminants should be identified and compared at the molecular level; there have been comments made about the use of biochemical tests and whether they can give a clear ID. Something to think about.

There has been movement in the area of harmonising the various Pharmacopoeia. In the Pharmeuropa April 2000 the proposed text for the harmonised method was published for public comment. The text has not been incorporated into the EP 2001 so it can be concluded that the text is still under consultation.

There is one significant change in the harmonised text – it is proposed that the incubation period for products terminally sterilised with steam, and that are tested by the direct inoculation method is reduced to 7 days. It is not clear why the incubation period is dependent on the process of manufacture or the test method used – if the authors have concluded that 7 day incubation is adequate to recover stressed cells then it is perhaps irrelevant where the stressed cell comes from.

Once again there appears to be a lack of clarity. To my knowledge there will not be a lot of products that are terminally sterilised AND require the direct inoculation method. Remember that the stated method of choice is the membrane filtration method – it is a reasonable assumption that the majority of terminally sterilised products will be tested using the membrane filtration method. If this provision remains in the harmonised text there will perhaps be limited application in practice.

There is a need to review the whole of the proposed harmonised text, almost line by line, with respect to the current EP 2000 to appreciate some of the subtle changes in emphasis that have been included in the harmonised text. Such a review is attached. It is worth reviewing your own practices against this proposed text as it could be the next version that you will have to comply with.

When thinking about the future of the sterility test one comes back to the question – what value and benefit is gained by conducting the sterility test? What assurance is provided?

The concept of Parametric Release, that is making a batch release decision based on parameters rather than finished product testing, has been in place for many years. In the last 18 months there have been three draft documents published in the Europe that deal with Parametric release – with a particular focus on elimination of the sterility test.

There is a document intended for assessors (CPMP / QWP / 3015 / 99 draft), one for inspectors (PR 2/99-1 Draft 8.1) and one for manufacturers (EU GMP Annex 17 draft). Essentially these documents give the basis for applying and gaining approval for Parametric Release for Terminally sterilised products. The emphasis is on the manufacturer having in place a robust sterility assurance system – irrespective of whether the it has, or intends to apply for, parametric release. I would strongly recommend that if your company manufacturers terminally sterilised products that you familiarise yourself with these documents because it is clear that the content describes the direction that the authorities are going (certainly here in the UK).

There is little that is new in these documents – all the sterility assurance system elements practiced today remain; what is new is the requirement to formally conduct a risk analysis of releasing non-sterile product to the patient - to know the failure modes within the process, know that they will be detected if they occur and to have procedures that describe the corrective action that will be undertaken. The emphasis is on demonstrating robustness – this is nothing new because as we all know the sterility test, certainly for terminally sterilised products, does not provide assurance of the capability of the process.

For the future the harmonised text for the sterility test will, eventually, be incorporated into the Pharmacopoeia, the issues with respect to the sample size and the insensitivity of the test will remain. For terminally sterilised products maintaining momentum in progressing to Parametric release is an appropriate direction to be taking.



Diary Dates

10th & 11th April: Practical Training on Cleaning & Disinfection, University of Bath
(see page 13 for more information)

15th May: Day Visit to Reading Scientific Services Ltd in Reading
An agenda and application form will be sent out shortly. Places will be limited on a 'first come first served' basis

17th & 28th November: The PharMIG Conference and AGM, Peterborough Moat House Hotel
(see page 14 for more information)

PharMIG Office Update

Just to let everyone know that maternity cover for Poly has been sought and found! Gina Bretti will start training on 3rd April with Poly who will be going off on maternity leave mid May.

Also, some of your accounts departments are still sending letters and cheques to the old address. Please ask them to change their database information:

PharMIG, Unit 72B, The Maltings, Roydon Road, Stanstead Abbots, Herts ,SG12 8HG
Tel: 01920 871999 Fax: 01920 871156 Email: poly@pharmig.org.uk

Finally, any financial queries can be sent to Jan Baldwin our Accounts Administrator at the PharMIG office. You can email her on info@pharmig.org.uk.



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