



PharMIG news

Chairperson's Review

It seems impossible to me that more than a third of 2003 has gone, especially that Easter has already passed - and it is time for another newsletter. I'm often told that as you get older time passes quicker but the worrying thing is that my 12 year old daughter is also making comments about how quick the year is going - I think in her case it's more "time fly's when you're having fun!" What do you think? I like to think the latter.

You should all be aware that Maxine Moorey has been appointed full time by PharMIG with responsibility for Business Development. I am sure you have noticed the increase in communication with you the Members particularly by e-mail, making you aware of what is coming up and also seeking feedback on what PharMIG should be focusing on for the future. Maxine brings a wealth of experience from commercial marketing of conferences and a great deal of enthusiasm - I am confident that with her drive and commitment that PharMIG will grow to be all that it can be. Poly Hajjipieris has also returned from maternity leave and will be working with Maxine in the office. If you have any questions, comments, concerns then the office is your first point of call.



With the growth of PharMIG more office space was needed - so the office has moved. The new address can be found in this Newsletter and on the PharMIG website. There is no change to the contact numbers. Another exciting development is the PharMIG website - there has been behind the scenes activity to improve the site so I would strongly encourage you to surf the net and have a look, and bookmark for easy access in the future.

One of the challenges that face the PharMIG Committee is time pressure -juggling the inevitable conflict between the "Day Job" and PharMIG activity. However both the Committee and I are committed to ensuring that the programme of events that has been developed for 2003, with in-put from PharMIG Members, is delivered. To date you will have seen the benefit of this increased focus but if you feel in a position to give of your time to support the Committee then let the office know, your call will always be welcome.

Also to date in 2003 there has been a very successful, over subscribed, visit to CP Pharmaceuticals in Wrexham. Our thanks go to CP for their hospitality. Site visits were more frequent in the past, but there has been limited activity in this area for the past couple of years. As the CP visit clearly indicated there is still a lot of interest from the PharMIG Members - ask yourself whether you are able, or would like to host a site visit from PharMIG and let Maxine know.

Keep supporting PharMIG so PharMIG can support you. Until the next time.

Sharon Johnson - Chairperson PharMIG

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Commentary: The Changing Role of the Pharmaceutical Microbiologist

By Tim Sandle, BPL

A shift of seismic proportion is happening...but there is no need to gaze down at your feet. The role of the Pharmaceutical Microbiologist is slowly shifting from the perplexed tester to the perplexed risk assessor.

I've watched this change, from my vantage point, over the past fifteen years. From when I began my career in microbiology as a bottle washer (well, my first task in a Microbiology lab was removing labels from media bottles which were to be recycled) to my current role heading up the microbiological function at BPL.

Whether this change is driven by regulators or by QA or by microbiologists themselves, struggling to complete a massive programme of work offset against struggles to purchase equipment and the continual juggling of human resources, is arguable. What is clear is that there has been a shift of emphasis from testing towards risk assessment; from the pharmaceutical microbiologist at the bench (chained or otherwise) to the pharmaceutical microbiologist out in the factory.

The current ethos is to spend less time testing and accumulating a mass of data which is never properly analysed or studied for trends, towards more time formulating corrective and preventative actions and performing microbiological risk assessments.

The microbiologist is now called upon to have a far greater knowledge of physical parameters. For example, can the significance of results from a clean room, whether viable micro-organisms or non-viable particles, be truly understood without an understanding of other physical parameters? Physical tests, such as pressure differentials, clean-up times and airflows frame the context of the microbiological result. Likewise the microbiologist is required to have a greater understanding of engineering and engineering systems. For example, in assessing the results from a purified water system some knowledge of flow rates, valve design, re-circulation, heating and piping is required.

Once a sample has been read and speciated (and been taken through a reasonably lengthy confirmation that it is not a laboratory error) further evaluation is required as part of the out-of-limits procedure. OOL is a more preferable term than out-of-specification: it is an anathema to the microbiologist to be told that one erroneous surface RODAC plate result is an OOS! Old philosophies of test, re-test (and carry on re-testing) until a satisfactory result is obtained are redundant approaches or much reduced in emphasis. The new language is that of risk assessment.

The types of risk assessment that the microbiologist is required to become involved with are either an assessment of the significance of an above action level result where corrective and preventative actions (CAPA) are employed. Or, more commonly, an assessment of the controls and measures in place to ensure that the above action result does not occur in the first place. In other words being proactive rather than reactive.

Tools for performing such assessments include risk analysis tools borrowed from other industries or professions including HACCP (hazard analysis critical control points) from the food industry; FMEA (failure modes and effects analysis) and FTA (fault tree analysis) taken from engineering industries, such as, car production.

These approaches share a number of things in common:

- Constructing diagrams of work flows
- Pin-pointing areas of greatest risk
- Examining potential sources of contamination
- Deciding on the most appropriate sample methods
- Helping to establish alert and action levels
- Taking into account changes to the work process / seasonal activities

In order to understand these and to assess them it is important that the microbiologist builds up detailed knowledge of the production system and processes and gets to walk around the factory and manufacturing environment.

An example of using these approaches can be applied to environmental monitoring in establishing a testing regime:

- Monitoring in areas which have a more 'dirty' activity taking place in an adjacent room
- Varying the frequencies for surface monitoring compared to viable air monitoring
- Examination of the movement of people (corridors and changing rooms are often routes of the spread of contamination and a monitoring programme may focus more heavily on these areas)
- Assessing routes of transfer / in-coming goods
- Focusing on key areas like component preparation
- Having higher frequencies of monitoring for areas at ambient temperature with high amounts of water compared to cold rooms
- Intensifying monitoring towards final formulation / purification / secondary packaging / product filling
- Establishing a monitoring programme designed to test the effectiveness of cleaning regimes
- More frequent monitoring for open, compared to closed, processes
- Monitoring areas of potential contamination, for example door handles

One approach may be to establish a 'criticality factor' where different rooms, with different activities, can be rated. Therefore one room, where product purification takes place, would be given a higher criticality factor and be monitored weekly whereas, a wash-up area, would be given a lower criticality factor, and be monitored monthly.

Therefore, in my view, the role of the pharmaceutical microbiologist has changed. Many of the techniques for testing remain the same but it is the way that the data is used and the necessary pre-thinking before the testing begins which is different. The only thing lagging behind is the status of the microbiologist in the organisation. This person, one most able to offer a global view and to assess the impact of process and contamination risk, is too often found hidden in the laboratory.

(Tim has written this piece in a personal capacity and these views do not necessarily reflect the position of BPL).

Tim Sandle
Microbiologist
Bio Products Laboratory

Date for your diary

Sterility Assurance in Practice - Tuesday 8th July 2003

Hertfordshire Moathouse, Hertfordshire

09.30 – 10.00

Registration and Tea / Coffee

10.00 – 10.15

Sterility Assurance System
An overview of the elements

10.15 – 11.15

Conducting a Risk Assessment of Sterility Assurance Systems – a roadmap

This session considers the individual elements of a generic sterility assurance system and will be interactive. It will provide you, the delegate, with an approach that can be readily applied in your facility

11.15 – 11.30

Tea / Coffee Break

11.30 – 12.30

FDA Aseptic processing concept document – what is the impact?

12.30 – 13.45

LUNCH

13.45 – 14.45

Parametric Release Annex 17 – a practical application

14.45 – 15.00

Tea / Coffee Break

15.00 – 16.00

Open Discussion Session

Do you have specific topics that you want addressed in this forum? If so, send you questions in advance to the PharMIG office or hand them in at registration on the day.

16.00 – 16.15

Summary and Close

Fee:

£350 Members
£400 Non Members

Contact Maxine Moorey on 01920 871 999 or email info@pharmig.org.uk for more details.

Update from the PharMIG Office



We are working like mad on the 2003 Conference Programme plus, we have put on an additional course, not previously outlined in the Schedule sent to you, on 'Sterility Assurance in Practice' in July. Keep your eye out for that programme in this newsletter. I will be mailing you a hard copy shortly.

And, (see I told you that a lot has happened already this year), we are revamping our website. Unfortunately our Webmaster, Martin Sarosi, who put the original site together and ran it for PharMIG up until very recently, on a voluntary basis has now moved on to pastures new. We would like to say a HUGE thanks for all his effort and time in keeping the site running. With no webmaster, we then had to decide how to manage the site. The Committee agreed that as it was such an important communication medium, we should pay a professional company to manage it for PharMIG. So, I am happy to announce that Preview, the company that does the artwork for the newsletter, will be managing the site.

Dear All,

Where do I start? So much has happened in such a short space of time....

Firstly – I would like to officially welcome back Poly. She started back 2 days a week in January. After time off on maternity leave it took her a few weeks to get back into the swing of things. Now, she has relaxed back into her role and is providing me with invaluable information on the background of PharMIG, as well as the day to day general stuff. Together we have been sorting out all the complicated 'techy' admin side of running a company, as well as sorting out some of the meetings that will be running in the last quarter of this year. In addition to her skills and experience that she has brought back to PharMIG, for me personally, it's like having a breath of fresh air in the office. Its great to be able to (on rare occasions of course) sit back with a cuppa and put the world to right – oh what fun we have.

I have also been taken on full-time by PharMIG which is great and, I feel very proud to have been invited to join the Board of Directors. It feels good to be wanted and appreciated – you don't get that in many work environments I can tell you.

Also, with Poly back, we realised that the intimate rabbit hutch that we have been working in at 72B suddenly became just that little bit too small. So, we have moved! Not far though – in fact just literally next door to 71 The Maltings. The space here is HUGE and it has made our working lives much easier.

I am pleased to report that, to date, we are running almost on time with our schedule of programmes for 2003. In fact I have placed 3 programme outlines in this months newsletter which include 'Practical Approaches to Method Validation' (June 4th) and 'Practical Training on Cleaning and Disinfection' (September 03), which is now in it's 3rd year.



Well, I think that's it for now. I would hate to take up the entire newsletter with my waffle. I hope you found the above of interest though. If you have any questions or suggestions about any meetings / courses or anything else related to PharMIG, don't hesitate to give me a call or send an email.

Hear or see you soon,

Maxie

Business Development Director

we have moved...

Please note (and kindly pass on to your accounts department) PharMIG's new address:

71 The Maltings, Roydon Road. Stanstead Abbots, Hertfordshire SG12 8HG

(Telephone and fax numbers remain unchanged)

Editors Note

Dear reader,

God it's hard sometimes to find something to say to you! No inspiration, just a blank computer screen staring back at me, which suddenly gives me an idea. CFR 21 part 11 and all that computer software validation stuff. Well there is good news on the horizon for common sense as there's a proposal that this document should be interpreted differently so that in some circumstances when using computer systems your paper copy can be treated as your raw data – hooray! This may allow systems that you have unplugged and put on the shelf because they were not compliant to be used. Don't take my word for it check out document:

Guidance for Industry 21 CFR Part 11; Electronic Records; Electronic Signatures Maintenance of Electronic Records (Draft Guidance for Industry -- Not For Implementation)

at: http://www.fda.gov/ora/compliance_ref/part11/default.htm

Enough of one of my least favourite subjects and onto the newsletter. We have started a series of person profiles with this issue. These will allow you to find out what's behind that professional face of PharMIG; the Committee, Members and other people of interest and discover the true 'inner' person. I hope this will be entertaining for you and may even be useful in providing opening gambits when meeting people for the first time. I can just imagine people starting a conversation with "I was fascinated to read in the PharMIG Newsletter that you are an avid train spotter" er, well may be not!

Wish me luck I have the FDA with me for 9 days in June!



Paul Lovegrove-Saville
E-Mail: news@pharmig.org.uk

PharMIG Action Group



Natasha Gibbs
Action Group Co-ordinator

The current Action Groups are continuing to produce important data.

The Non-Sterile Monitoring Group Member, Julian Kay, presented the data from their first questionnaire at the joint PharMIG and PQG meeting held on the 28th January 2003 and received some very promising feedback. The Group are coming together to begin the preparations for a monograph.

The Bacterial Endotoxin Group leader Lynne has been working with the Parenteral Society to produce a joint monograph and we eagerly look forward to the publication of this document.

Trudy and her team on the Disinfectant Action Group have completed their sections for their monograph. The monograph is now out for review. They have had some encouraging feedback from their paper and we can look forward to its publication.

The Water Activity Action Group and Steam Sterilisation groups are actively seeking new Members so please get in touch.

The Action Groups are dynamic and do accept new Members. If you would like to know more information about any of the Groups mentioned or would like to participate in one then please contact myself on agc@pharmig.org.uk.

Wishing you all continued prosperity in the demanding field of Pharmaceutical Microbiology.

Pharmacopoeia Tests for Contamination in Raw Materials

A survey of current practice

K. O'Hagan (1) and B. Alexander (1) *

ABSTRACT

This article describes the current working practices of European pharmaceutical manufacturers' microbiological testing regimes of raw materials. Also highlighted are the inconsistencies within the European Pharmacopoeia with regard to the microbiological testing regimes and microbial limits assigned to raw materials.

1. INTRODUCTION

There are microbial limits for 43 raw material mono-graphs described in the European Pharmacopoeia (Ph. Eur.) [1]. The monographs describe the various testing requirements for compliance. Depending upon the raw material and its source, the microbiological requirements can include bacterial and fungal levels and absence of specific pathogens. However, the Ph. Eur. shows some inconsistency with regard to the tests specified and the microbial levels acceptable for the raw materials listed. In some instances testing refers to Total Viable Aerobic Count (TVAC) for a raw material, but for other raw materials testing for bacteria and/or fungi is required. Under the present mode of production, are these tests able to detect pathogenic organisms likely to occur in the product?

A test derived from a good study carried out long ago may have been efficient then, but no longer under present conditions of manufacture. Moreover, there are significant differences in the testing requirements for raw materials between the Ph. Eur. and the United States Pharmacopoeia (USP). The objective of the current International Harmonisation (IH) program for microbial contamination is to harmonise the methodology and replace the existing differing tests of the Ph. Eur., USP and Japanese Pharmacopoeia (JP).

However, based on the origin of raw materials in the three areas, is harmonisation possible? Historically some raw materials (e.g. starches) were assigned limits for both bacteria at 30-35°C and fungi at 20-25°C based on informed opinion and available data, whereas for others (e.g. gums) a total aerobic count limit at 30-35°C only was stipulated. Tests for *E. coli* and *Salmonella* were initially only applied to materials of animal/plant origin (known to be a potential reservoir of either or both), but some recent limits (e.g. polyhydric alcohols) are based on the USP and include both.

In 1999 the Pharmaceutical Microbiology Interest Group (PharMIG) carried out a survey of its members on the testing regime they adopted for raw materials used in the manufacture of pharmaceuticals. A follow-up survey was carried out in early 2000 asking the number of raw material batches that had failed the Ph. Eur. criteria. The PharMIG membership primarily consists of microbiologists working in British pharmaceutical quality control laboratories. This follow-up report describes the results of this survey and discusses the tests and the pharmacopoeial microbial limits of raw materials in the light of these results.

2. SURVEY RESULTS

52 questionnaires were sent out, 26 were returned with completed responses, 5 were returned as not a manufacturing site. The number of responses per question seldom added up to 26 as many sites had more than one response (i.e., manufactured more than one type of product). The majority of sites manufactured only pharmaceuticals.

All types of formulations and manufacturing were represented in the survey. There was no difference in the amount or type of raw material testing with the type of manufacturing (e.g. ethical, generic, and contract) or the microbial status of the finished product (sterile or non-sterile). The responses to the questions sent out to the PharMIG members are shown below.

2.1. SITE DETAILS

2.1.1. What type of products made?

Pharmaceuticals	23
Toiletries	5
Cosmetics	3
Devices	5
Detergent/disinfectants	1

2.1.2. Range of products on one site

Pharmaceuticals only	16
Pharmaceuticals plus others	7
Devices only	2
Toiletries/cosmetics only	1

2.2. PRODUCT DETAILS

2.2.1. Formulations made?

Product form	Number	Non-sterile	Sterile
Liquids	19	18	9
Creams	8	10	1
Ointments	6	7	2
Powders	7	6	2
Devices	6	5	3
Granules	3	5	0
Tablets	10	11	0
Capsules	9	10	0
Other*	3	3	2

* Other included gels, aerosols, injectable copolymers.

2.2.2. Type of manufacturing?

Generics	10
Ethical	12
Contract	12
Other*	4

* Other included pilot scale, bulk and diagnostic manufacturing.

2.3. NON-STERILE PRODUCTS MADE ON-SITE?

Yes	23
No	3

2.3.1. Non-sterile products tested for microbiological contamination?

Non-sterile Formulation	Test All	Test some	Test none
Liquids	12	6	0
Creams	7	3	0
Ointments	4	2	0
Powders	1	4	2
Devices	2	7	0
Granules	1	3	0
Tablets	1	10	0
Capsules	0	9	0
Others	2	2	0

Very few sites carried out no testing on non-sterile products. The only instance was with powders. Most sites tested all liquids, some tablets and some capsules.

2.3.2. Raw materials used in these products tested for microbiological contamination?

All materials	0
Some materials	25
No materials	1*

*Device manufacturer.

These results show that the decision to test some materials is independent of the type of manufacturing.

2.3.3. What factors influenced the decision to test raw materials?

In this question responders were asked to rank answers from 1-11 in order of importance, 1 being least important and 11 being most important. These values were totalled giving an overall ranking of factors. Numbers in brackets indicate the number of companies which ranked this factor as their most important. Numbers in brackets do not add up to 26 as some responders ticked rather than ranked. Where this happened every tick scored five, every blank scored zero.

External regulatory requirements (3)	152
History of contaminated raw material (1)	120
Internal company policy (2)	118
Depends on the raw material intrinsically (1)	117
Depends on the route of administration of the final product (4)	97
Raw material supported growth (1)	88
New supplier (0)	83
Depends on sales market for finished product (0)	69
History of contaminated product (1)	64
New product introduction (0)	61
Final formulation supported growth (0)	59

2.4 STERILE PRODUCTS MADE ON-SITE?

Yes	13
No	13

2.4.1. Sterilisation process?

Aseptic processing	12
Terminally dry heated	3
Irradiation	4
Terminally steam heated	8
Ethylene oxide	2

2.4.2. Raw materials for sterile products tested for microbiological contamination?

Yes	10
No	3

What tests?

Sterility tests	2
Total Viable Count	11
Specific pathogens	7

Does the method of sterilisation influence the decision to microbiologically test raw materials for microbial contamination?

Sterilisation Process	Sterility test	Total viable count	Specific pathogens	Not tested*
Aseptic processing	2	10	6	2
Terminally dryheated	0	3	1	0
Irradiation	0	3	1	1
Terminally steam heated	2	8	5	0
Ethylene oxide	0	2	0	0

*Where no testing occurred, one was a blow fill seal product, one was a biological product, one company performed a bioburden test on finished product prior to irradiation. One site commented that the only raw material tested was water.

Where only sterile products were manufactured (3 replies), total viable counts were performed on raw materials (2 sites) and parametric release was carried out on raw materials (1 site).

2.5 MICROBIOLOGICAL TESTING OF RAW MATERIALS

2.5.1. Is TVAC performed on raw materials?

Yes	26
No	0

What method?

Ph. Eur.	15
Ph. Eur. - modified	4
Other pharmacopoeia	3
In-house method	4

What limits are applied?

Same (pro rata) as finished product	5
Depends on source (organic/synthetic) of material	11
Depends on results from previous lots	1
Other	8

2.5.2. Are enrichment tests carried out for specified micro-organisms?

Yes	16
No	7

What method?

Ph. Eur.	9
Ph. Eur. - modified	6
Other pharmacopoeia	1
In-house method	1

What limits are applied to the results?

Same (pro rata) as finished product	9
Depends on source (organic/synthetic) of material	6
Depends on results from previous lots	1

2.5.3. Are isolated organisms classified according to severity (e.g. forbidden, objectionable, permitted)?

Yes	9*
No	6

*All 9 sites classifying the isolates used Ph. Eur. classification i.e. E. coli, Salmonella, Staphylococcus aureus and Pseudomonas aeruginosa.

2.5.4. Is data from these tests analysed statistically or trended?

Yes	2
No	13

SUMMARY OF RAW MATERIAL TESTING PRACTICES

- Usually testing was by Total Viable Aerobic Count (TVAC) using the Ph. Eur. method.
- 70 per cent of those performing TVAC also tested all raw materials by enrichment for specified micro-organisms using the Ph. Eur. method and the Ph. Eur. classification for "absence" organisms
- The limits tended to be in-house based on the origin of the material and the intended use of the product.
- Factors influencing the decision to test raw materials were varied: the main factors were the response to external regulatory requirements and the formulation of the final product (i.e. wet/dry, sterile/non-sterile).
- Where the material was to be used for sterile product manufacture, the justification for not testing the raw materials was parametric release or bioburden testing prior to sterilisation. The testing of raw materials for sterile products tended to be TVAC rather than sterility or enrichment tests.

2.6. CONTROL OF RAW MATERIAL SUPPLIERS

Many companies had shared responsibilities for the functions listed below. Hence more than 27 answers were given for each question.

2.6.1. Do you have a list of approved suppliers?

Yes	26
No*	1

* Currently under review.

2.6.2. Which department maintains this list?

Quality assurance*	19
Purchasing*	12
Quality Control	10
Regulatory	1
Production/manufacturing	0

* Quality Assurance includes Compliance and Quality Standards groups, Purchasing includes Commercial and Procurement groups

2.6.3. Which departments influence/control this list?

Quality assurance	16
Purchasing	10
Quality Control	8
Regulatory	0
Production/manufacturing	2

2.6.4. How often are these suppliers audited?

Every year	2
Every 2 years	10
Every 3 years	1
Every 4 years	1
Every 5 years	1
Varies with material/problems	6
Infrequently	4
Never/don't know	1

2.6.5. Which department organises the audits?

Quality assurance	21
Purchasing	6
Quality Control	4
Regulatory	0
Production/manufacturing	0

2.6.6. Are the test results from the supplier's, certificate of analysis taken in lieu of in-house testing?

Yes	24
No	3

Are suppliers' test results analysed statistically?

Yes	2
No	22

Are microbiological tests on raw materials audited or spot checked?

Yes	11
No	11

2.6.7. How is a new material (from a supplier who is approved for other materials) introduced

Test 5 batches of new material	2
Test 3 batches of new material	7
Laboratory testing (number of lots not defined)	5
Supplier audit and process validation	2
Audit and supplier history	1
Varies with material	1
Procedure outside immediate group	5
Not known	3

2.6.8. How is a new supplier (new or existing raw material) introduced?

Same process as with new material	8
Test 5 batches of new material	1
Test 3 batches of new material	1
Test batches and supplier audit	6
Test 5-10 batches of new material	1
Procedure outside immediate group	5
Not known	3

CONTROL OF SUPPLIERS OF RAW MATERIALS

- All sites, except one which was under review, had a list of approved raw material suppliers. This list was controlled/administered by Quality Assurance (QA) and purchasing in most cases.
- The majority of sites audited their suppliers every two years. The audits tended to be a QA rather than a purchasing function.
- Most sites took data from the raw material supplier’s certificate of analysis.
- 50 per cent of the sites performed spot/audit tests on the raw materials tested by suppliers.
- There was a range of responses as to how new material/suppliers were admitted to approved status. Where the responder knew the process, it was usually via audit and testing 3 lots of materials.
- A number of responders commented that microbiologists were not usually involved in the supplier approval process – it tended to be Chemistry testing only that gave a supplier approved status. However, poor microbiology results could result in approval being rescinded.

2.7 SHOULD MICROBIOLOGICAL TESTING OF RAW MATERIALS BE REVIEWED?

No change i.e. no Ph. Eur. monograph requirements	2
Included in Pharmacopoeia monograph	3
Included in Pharmacopoeia “information and guidance”	9
Recommended industry standards published	15
Other	1

There was a desire to see Pharmacopoeial harmonisation.

3. DISCUSSION

3.1. RAW MATERIAL TESTING PRACTICES

The responses indicate that the testing practices were fairly consistent across the industry with most sites following the Ph. Eur. guidance or the relevant monograph.

Most companies tested their raw materials whether or not there was a monograph specifically requiring testing. In most cases a risk analysis was performed so that the risk of a contaminated material contaminating the finished product was assessed.

An example of this risk analysis process is shown in Figure 1. Most companies, once familiar with the material and supplier, reduced the frequency of testing. When this occurred the supplier’s results were often taken as the “in-house” results.

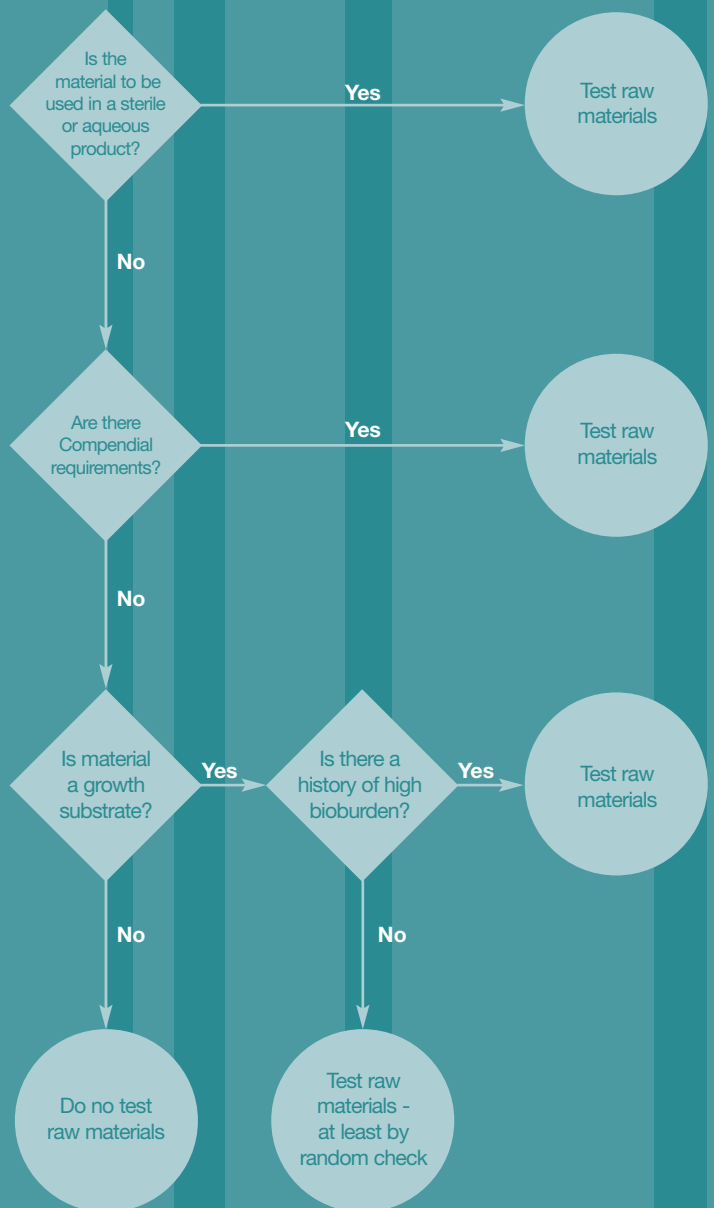


Figure 1 — Microbiological testing of raw materials - is it required ?

Quality assurance and purchasing had a major role in organising and choosing raw material suppliers. The most common audit frequency was every 2 years. In about half the sites the responsibility was shared between departments.

Testing practices varied considerably from site to site. Generally, data was taken from the certificate of analysis, was not analysed statistically and spot checks of materials was carried out at 50% of sites. There was little difference in the introduction process for new materials from new suppliers. All responding sites tested a number of lots of the new material prior to its use in manufacturing, some supplier audits took place. The supplier audit was more common with the introduction of a new supplier than with the introduction of a new material from an approved supplier.

3.2. RAW MATERIAL BATCH TESTING

The purpose of the follow-up survey was to determine how many of the tested lots had failed the Pharmacopoeia tests, i.e. to assess whether the limits and testing requirements described in the Ph. Eur. were appropriate for present day production of raw materials.

However it must be borne in mind that these are the raw material user test results not the raw material supplier test results. Consequently the assumption has been made that these results are from materials that have passed the supplier's microbiological testing. All sites tested raw materials for TVAC.

About 70 % tested raw materials using specific enrichment methods. Where testing occurred, the majority of sites used Ph. Eur. methods and classification of isolated organisms. The limits for both types of testing were approached more pragmatically, with the limits being dependent on the source (synthetic/organic) of the raw material or its end use. Very few sites statistically analysed or trended data from either tests.

Table 1 lists 43 raw materials with existing or proposed microbiological tests and specifications in their monograph. It is evident from Table 1 that the testing requirements vary between total count, bacteria and fungi.

The survey asked members for the number of lots of raw materials tested in 1999 and the number that failed the monograph requirements. In total 1446 lots were tested, obtained from the production of 29 raw material products. 22 of these 1446 lots failed the requirements of the Ph. Eur. and 9 lots failed the test for Enterobacteriaceae; of these 9 lots 3 also failed the test of the Ph. Eur.

Table 1 indicates from which products these failing lots were taken, and also the total number of lots of these products which were tested. Some products showed a relatively high rate of failure compared to the general rate found with the 29 products tested.

For all 29 products, 22 (2 lots of tragacanth not included) out of 1446 lots tested gave a positive Ph. Eur. test, or 1.5%. For magnesium stearate, 4 out of 41 lots failed the Ph. Eur. test or 9.8% and for the 141 lots of sorbitol, 6 gave a positive test or 4.3%. Inclusion of the non-pharmacopoeial test for Enterobacteriaceae indicates that not 22 but 31 lots gave a positive test for the 1446 lots tested or 2.1 %; the test was not positive for any of the 41 lots of magnesium stearate tested, neither for any of the 141 lots of sorbitol.

Including the 2 failed lots of tragacanth, 33 lots in total of the 1446 tested, or 2.3 %, failed the microbiological criteria for raw material testing. Unfortunately the actual counts obtained for the failed lots could not be obtained. This information would have been useful in order to estimate the sensitivity of the testing, i.e., the percentage of contaminated lots likely to be detected by the control test.

4. CONCLUSION

The pharmaceutical industry, as a whole, takes a rational response to the amount of testing performed based on a historical view of the results, suppliers and end product usage of the raw materials. The surveys have shown data that can provide an accurate or 'true' marker for the testing requirements and specifications for raw material used in the pharmaceutical industry. The lot testing survey has shown that the current Ph. Eur. requirements for microbiological testing of raw materials need to be reviewed.

This survey shows very few failures in either the quantitative or qualitative microbial tests. As the majority of the specifications were met, consideration should be given to reducing the limits to a more realistic level. This process review is common practice under the principles of Good Manufacturing Practice (GMP). Where limits are applied, such as regulatory or in-house, and these limits are consistently being achieved they are critically assessed and in some instances reduced with justification.

However actual counts would greatly assist the study in providing supportive data to give an indication of the proportion of lots that would fail any revised limits. Furthermore, the Ph. Eur. should also consider consistency with regard to the testing requirements. It is clear that some raw materials are tested for bacteria and fungi whereas others are tested for Total Viable Aerobic Count.

This inconsistency should be removed. Similarly, surveys of this type provide valuable information on the need for harmonisation of raw material monographs in the Ph. Eur. and USP. It would be useful for US pharmaceutical microbiologists to carry out a similar survey to determine 'true' data for comparison with this survey. An extension of this study should be considered in order to set appropriate testing practices and specifications for raw materials in guiding the international harmonisation for microbial contamination towards their aim.

5. REFERENCES

- [1]. European Pharmacopoeia (Council of Europe, Strasbourg, France, 4th Edition, 2001).
- [2]. Sugar spheres, monograph 1570, Pharmeuropa 10, 688-689 (1998).

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Table 1. — Results of Microbiological Testing of Raw Materials

Material	No. lots examined	Number of lots exceeding specifications in this aspect (current Ph. Eur. limit in italics for microbial counts)					
		TVAC	Bacterial Count	Fungal Count	Absence of E.coli in 1g	Absence of Salmonella in 10g	Absence of Enterobacteria and other G -ve bacteria in 1g
Acacia	30	<i>10⁴ 0</i>			0		1*
Agar	22	<i>10³ 1</i>			0	0	
Alginic acid	10	<i>10² 0</i>			0	0	
Aluminium oxide	3	<i>10³ 0</i>			0		0
Bentonite	5	<i>10³ 0</i>					
Calcium gluconate	0	<i>10³</i>					
Calcium stearate	8	<i>10³ 0</i>			0		
Cellulose, microcrystalline a	0	<i>10³</i>		<i>10²</i>	0	0	
Cellulose, powdered a	74	<i>10³ 0</i>		<i>10² 0</i>	0	0	
Charcoal, activated	0	<i>10³</i>					
Dextran 40/60/70 for injection	0	<i>10²</i>			0		
Ferrous gluconate	2	<i>10³ 0</i>					
Frangula bark dry extract	0	<i>10⁴</i>		<i>10²</i>	0	0	
Galactose	0	<i>10²</i>					
Gelatin	124	<i>10³ 0</i>			0	0	
Glucose, spray-dried	1		<i>10³ 0</i>	<i>10² 1</i>	0	0	
Guar	0	<i>10⁴</i>			0	0	
Kaolin	23	<i>10³ 0</i>					
Lactitol c	0	<i>10³ 0</i>			0	0	0*
Lactose, anhydrous	164	<i>10² 0</i>			0		
Lactose monohydrate	0	<i>10²</i>			0		
Lactulose	123	<i>10² 0</i>			0		
Magnesium stearate	41	<i>10³ 4</i>			0		0*
Maize starch	173		<i>10³ 1</i>	<i>10² 2</i>	2		2*
Maltitol	9		<i>10² 0</i>	<i>10² 0</i>	0	0	
Maltodextrin	28		<i>10³ 0</i>	<i>10² 1</i>	0	0	
Mannitol	20		<i>10² 0</i>	<i>10² 0</i>	0	0	
Pancreas powder	0	<i>10⁴</i>					
Pepsin powder	0	<i>10⁴</i>					
Potato starch	6		<i>10³ 0</i>	<i>10² 0</i>	0		1*
Rice Starch	4		<i>10³ 0</i>	<i>10² 0</i>	0		
Senna leaf dry extract	0	<i>10⁴</i>		<i>10²</i>			
Sodium alginate	1	<i>10³ 1</i>			0	0	
Sodium starch glycolate type A&B	101				0	0	
Sorbitol	141		<i>10² 6</i>	<i>10² 0</i>	0	0	0*
Starch, pregelatinised	75		<i>10³ 1</i>	<i>10² 0</i>	0		4*
Sugar spheres d	7		<i>10² 0</i>	<i>10¹ 0</i>	0	0	
Talc (oral use)	180		<i>10³ 1</i>	<i>10² 0</i>			
Talc (topical use)			<i>10² 0</i>				
Tragacanth	31	<i>10⁴ 1</i>		<i><10³ b 2</i>	0	0	
Trypsin	0	<i>10⁴</i>					
Wheat starch	4		<i>10³ 0</i>	<i>10² 0</i>	0		
Xanthan gum	36		<i>10³ 0</i>	<i>10² 0</i>	0		1*
Totals	1446	7	9	6	0	0	9

* Not a Pharmacopoeial requirement

a. Also complies with the test for Staphylococcus aureus and Pseudomonas aeruginosa.

b. PharMIG member in-house limit for fungal count for Tragacanth of 10³.

c. Also complies with the test for Pseudomonas aeruginosa.

d. Limits for the draft monograph [2] when the survey was performed and do not correspond to current specifications.

Profile - Professor Stephen Denyer



The serious part...

Professor Stephen Denyer graduated as a Bachelor of Pharmacy (1975) with First Class Honours from the University of Nottingham where he also obtained his PhD (1979), subsequently joining the staff of the Nottingham School of Pharmacy as Lecturer in Pharmaceutical Microbiology.

After 12 enjoyable years, he moved (1991) to Head the Department (now School) of Pharmacy at the University (formerly Polytechnic) of Brighton as Professor of Pharmaceutical and Applied Microbiology.

Industry recognition

Professor Stephen Denyer has been awarded the Royal Pharmaceutical Society Charter Gold Medal for 2003. This award, the pharmacy profession's highest honour, is given by the Society's Council on the personal recommendation of the President. It is awarded for an outstanding contribution to the profession or the Society nationally and was presented at a formal ceremony on the 14th May at the Society headquarters in London.

Professor Denyer commented that he was surprised and delighted to be recognised in this way for contributions he so willingly gave. The award, he said, was a testament to all those colleagues whose support and insight had helped him in his career in pharmacy education. There was no greater honour than being recognised by one's peers."

The family background

Married to Angela, who has shared my life for 28 years (and I've had the better deal), with two daughters, Karen (21 years) and Claire (19 years).

Karen is currently studying for a PhD in molecular genetics and Claire is in Belize for a GAP challenge teaching placement before going to university to study Zoology.

Profile - Professor Stephen Denyer

The Steve Denyer that you didn't know about...

What did you want to be when you were growing up?

A research scientist from the age of 10 when my friends brother returned from his first year at Cambridge University with more knowledge than I ever believed possible.

Did you like science at school?

Chemistry was great, fuelled by enthusiastic staff particularly a visiting teacher from Czechoslovakia. I dropped Biology at the age of 14 because of a timetable clash with a German language course. I was advised that I needed German to study Chemistry, one of the worst pieces of advice I have ever received. This meant that I became ineligible for a medical degree (mind you, my fear of taking blood was probably an insurmountable barrier to that career!) My physics teachers offered the most uninspiring insight into their world, which still colours my appreciation of that subject.

What is your earliest memory of a scientific experiment going wrong?

When I connected rubber tubing to a gas tap and blew down it and then watching the lighted burners of my fellow pupils going out sequentially down the bench at a critical stage of laboratory experimentation. Or, was it the time when we watched the gradually expanding balloon attached to a dripping tap that was placed just behind the teacher who was demonstrating the compressibility of gases... And then, of course, there was the occasion when I rode my racing bike with ignited sodium chlorate and sugar packed into the handlebars...I've never dismounted so quickly!

Do you have time for hobbies? If so, what are they?

I enjoy repairing cars and, with both daughters running vehicles, I could have up to four to maintain, none younger than 10 years old...but there's never enough time!

I am an assessor for the Institute of Advanced Motorists and can usually be found training an associate at some time during a weekend.

When was your first trip abroad with work and where did you go?

1981 to Florence in Italy - and I fell in love with the city!

How many countries have you visited in both work and holiday trips?

I've never counted, but far more for work than holiday.

What is your favourite country and why?

Italy, because of Florence and the Italian people.

What is your favourite drink?

A good malt whisky taken in good company at the end of a busy week.

What is the most unusual meal you have eaten?

I guess it has to be a student compilation of marmite, cheese, jam and crisps in a single sandwich - a staple food between the years 1972 to 1975! My tastes are a little more sophisticated nowadays!

Were you a teenage fashion freak?

Never!

Do you like music? What is your musical taste?

I like music, but I cannot make music (or so I am told). I apparently have the ability to confuse words and tunes to create irreproducible medleys.

I once had a near death experience in Paris while my wife was singing in a choir. The assistant who turned the pages of the music for the organist had not arrived and I was asked to assist. I can't read music but my solution was to look for the panic in the organist's eyes!

What is your favourite participative and spectator sport?

I don't have one, but if I did it would be motor sports.

If you could change your career at this stage in your life what would you do next?

An engineer, and then perhaps I could get to see some real value in physics!

Date for your diary

Practical Training on Cleaning & Disinfection

Tuesday 23rd & Wednesday 24th September 2003

The University of Bath, Claverton Down, Bath

PROGRAMME

Tuesday 23rd September

09.30 – 10.00	Registration & Tea / Coffee
10.00 – 10.15	Welcome & Introduction Dr Rosamund Baird
10.15 – 11.15	Disinfection Theory Dr Anthony Smith
11.15 – 12.30	Disinfection in Practice – Sterile & Non-Sterile Areas Rachel Blount
12.30 – 13.30	Lunch
13.30 – 14.15	CIP – Review of Accepted Practice and Current Standards Andrew Provan
14.15 – 14.45	Disinfectant Challenges in Hospitals and Home Dr John Barker
14.45 – 15.15	Tea / Coffee
15.15 – 17.30	Practical Demonstrations & Laboratory Work: Environmental Monitoring Monitoring Disinfectant Concentrations Testing of Skin Disinfectants – EN1499 and EN1500 Filter Integrity Testing Microbiological Aspects of Disinfectant Validation Rosamund Baird, John Barker, Rachel Blount, Lorna Simpson, Kim Morwood, Stuart Morgan, Stuart Rolfe
17.30 – 17.45	Discussion
18.45	Reception drinks followed by Dinner

Date for your diary

Practical Training on Cleaning & Disinfection

Tuesday 23rd & Wednesday 24th September 2003

The University of Bath, Claverton Down, Bath

PROGRAMME

Wednesday 24th September

09.00 – 10.00

Disinfection Challenges of Water Systems
Dr Annette Ellison

10.00 – 11.00

Role of Monitoring in Contamination Control
David Wilson

11.15- 11.30

Tea / Coffee

11.30 – 13.00

Case studies:
Small working groups will discuss cleaning related issues and report back on a suitable course of action
Rachel Blount, Dr Rosamund Baird, Mr Andy Martin

13.00 – 14.00

Lunch

14.00 - 15.00

The Importance of Cleaning Validation to the Pharmaceutical Industry
Dr Ansley Crockford

15.00 – 15.45

Interactive Audit Workshop
Dr Robert Johnson

15.45 – 16.00

Tea / Coffee

16.00 – 16.15

Final Discussion and Depart

Fee:

£800 Members
£925 Non Members

Please note:

Fees include one nights accommodation and dinner on Tuesday 23rd September.

Contact Maxine Moorey on 01920 871 999 or email info@pharmig.org.uk for more details.

PharMIG Diary Dates - Events Schedule 2003

June 26th

IBA STERIGENICS

1 Day Site Visit

July 8th

Sterility Assurance in Practice

1 Day Meeting

September 23rd & 24th

Practical Training on Cleaning & Disinfection - Bath

2 Day Training Course

October

Rapid Microbiology Techniques

1 Day Meeting

Date & Venue TBC

November 18th & 19th

PharMIG 2003 Conference - St Neots

2 Day Conference

December

Engineering for Microbiologists

2 Day Training Course

Date + Venue TBC

Full details will be mailed in due course. In the meantime if you have any questions regarding the event schedule please do not hesitate to contact

Maxine Moorey on (T) 01920 871 999 (Email) info@pharmig.org.uk