

# PharMIG

The Pharmaceutical Microbiology Interest Group

# News

Issue 3 December 2000

PharMIG

The  
Pharmaceutical Microbiology  
Interest Group



## NEW MICROBIOLOGICAL METHODS ARE WE OFF-COURSE?

Dr Nigel Halls  
GlaxoWellcome

**Most of what you'll read in this article may seem like heresy! Read it though, and think about it, there might be some truth if you look hard enough.**

A number of pharmaceutical companies are evaluating new microbial methods. Most of their activities (excluding identification methods) has been focussed on methods which get quicker results than the conventional methods for testing for Sterility, quicker results for testing against Microbial Limit standards in products and water, and sometimes quicker results in environmental monitoring.

My thesis in this article is that speed of obtaining results is not of the essence - what we should really be investing our intellects, time and money in is parametric release and in non-destructive testing. Let us look at the perceived advantages of obtaining quick



results against parametric release and non-destructive testing. Why do we have a perceived need to obtain results more quickly than they are obtainable by conventional microbiological methods? Let's try these two answers for starters:

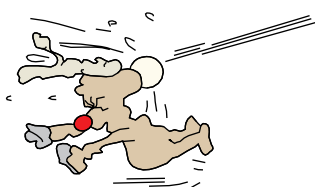
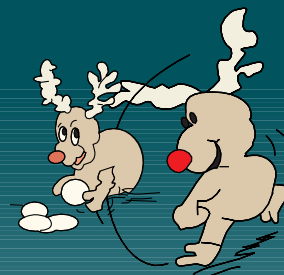
- Because our testing would present less interruption to the supply chain
- Because when things go wrong we would know about them in time to get them fixed immediately

We want rapid microbiological methods to present less interruption to the supply chain. I know a better way of presenting less interruption to the supply chain - its called parametric release! If we look at what our QA Microbiology labs are doing at this moment in time you will see that many of our products are parametrically released from a microbiological perspective - tablets for one! In many other cases we have "skip-lot" testing and maybe nine out of every ten batches have no microbiological testing interruption to the supply chain.

Surely we should be concentrating on the security of freedom from microbiological contamination of the other products which are not parametrically released by investing in improved control of our raw materials and in our production facilities and practices - in other words let's make sure they're not contaminated in the first place. Of course this pre-supposes that the regulators will go for this idea, and that needs influencing and persuading - if only half of the papers on rapid microbiological methods I saw presented at the Spring Meeting of the PDA had been presented on the topic of improved microbiological control of manufacture we might be a considerable way further towards parametric release being smiled upon by the regulators.

## In this issue

New Microbiological Methods are we off-course?	1
Chairmans Review	3
Members View on Stability Testing	4
Poem <i>The Rapid Microbiologists</i>	4
Setting Environmental Alert and Action Limits	5-7
Editors Note	7
PharMIG Action Group Update	8
Practical Training on Cleaning and Disinfection	9
Results of Survey on Biological Indicators	10-15
Patsy Petri-Dishes problem page for Microbiologists	16
Diary Dates	16
Cartoon	16



This seems so much like good sense to me that it demands the question - why are we investing in improved testing rather than fixing the problem at its source - in supply and manufacture? Microbiologists have a laboratory focus rather than a Production focus? Is because laboratory data is so much easier, neater, cleaner and less embarrassing to present than Production-based data? If anyone reads these pages I'm sure we'll be hearing other views. My view is that from a microbiological standpoint we're addressing the supply chain issue naively by putting our efforts into quicker test method let's put our efforts into getting such good control of manufacture that the regulators will want us to be releasing parametrically.

Anyway let's look at the supposed benefits and implications of obtaining rapid results from Microbial Limit Tests on finished products. We never question a satisfactory result and I don't suppose that's ever going to change. What are the options available to us when we get an unsatisfactory result? How is an instantaneous unsatisfactory microbiological result on a completed, filled packed product going to be any better than an unsatisfactory result 2-3 days later? The options are to reject the batch or to accept the batch (reworking is a comparatively rare option in pharmaceutical manufacture). Rejection is never taken lightly. In the "bad old days" what you did when you obtained an unsatisfactory result on a finished product was to re-test it (usually in duplicate) and pass the batch on the basis of the re-test. Now if re-testing was still allowed an instantaneous result would be a real asset, but sorry chaps the Barr Ruling, has put paid to all that. An unsatisfactory result means an investigation of laboratory practices and production practices and is most likely to take a lengthy period of time so the speed of obtaining the result becomes swamped by the time required to investigate its validity. I really don't therefore believe that rapid methods have a great deal to offer in this area.

Of course there is an argument that a rapid microbiological method could be used as an in-process test or as a screening test to decide on the need for a conventional Microbial Limit Test. Really! Should we be putting our money on an in-process test rather than on improving control of contamination in our manufacturing facilities, do we really want to be taking another step backwards from believing that we can actually validate and control our facilities? I should hope not!

We want rapid microbiological methods because when things go wrong we would know about them in time to get them fixed immediately. But can we? Let's look more closely at this idea. The two areas I want to discuss are water testing and environmental monitoring.

Water invariably meets the pharmacopoeia physical and chemical limits but it presents ongoing microbiological problems. Wouldn't it be great if we could get an instantaneous (or at least a very quick) read out of our water quality? Or would it? We all know we never question a satisfactory result, this is because a satisfactory result is what we expect because of all the effort we put into validation and process control.

So the issue of rapid testing of water comes down to whether it is better to know that we have an unsatisfactory result on the spot or two or three days

later. Either way the options are limited, they are to accept the data and take corrective action on the system, or to doubt the data and re-sample the water. My guess would be that the latter is the most usual response. This is because there are known errors associated with water sampling and testing - contaminated sample point, contamination by the sampler, contamination during testing to name but three. OK, if you have an instantaneous result you can in theory look back at the system exactly as it was when you left it (or two or three hours later because none of these techniques are really instantaneous). In practice testers never leave sample points in exactly the same state as they found them, they may have sprayed each of them with alcohol after the intrusion and would also have flushed a few dozen litres of water through them. Is a re-test two hours later going to divulge anything significantly different from what would be found two or three days later? Most often the repeat test whether done two hours later or two days later will be satisfactory and that will be the end of it.

This brings us to the point when the results continue to be unsatisfactory over several days or over several sample points - in the case of water these are not going to lead to accepting or rejecting water, they are to do with taking corrective action to the process or otherwise. Anyone who has ever worked with water purification and distribution systems knows that when you get a "bad" result it's not just a matter of twiddling the right knob on the system to get the problem fixed - in fact it can take days or even weeks for the effects of a corrective action on a water system to take effect and stabilise. So in reality as far as taking corrective action is concerned, it is probably neither here nor there that you have real time data on water or whether you have to wait 2 or 3 days for the data because of the far longer delay time for the corrective feedback action to kick in.

Here, for routine testing of water I would conclude that rapid testing does not offer sufficient advantages over conventional testing to compensate for the added capital and depreciation costs of rapid testing equipment. In truth I do not think this is necessarily the case when validating a new water system or troubleshooting a system which has gone so far out of control that there can be no reasonable presumption that samples are more likely to meet than to fail to meet the standards. This is a good case for rapid testing and getting instantaneous results - but really it should not be a situation requiring to be addressed too often. Could rapid microbiological methods of environmental monitoring give us better control in sterile manufacture? Here I'm not so sure. Let's go back to one of our first premises - if results are satisfactory we never question them, so we only have to deal with unsatisfactory environmental results. So what are the options?

When environmental results come 2-3 days after the event our options are very limited, they usually boil down to investigating the cause, cleaning it up and making sure it never happens again. Once in a while we may decide that the facility was not fit for sterile manufacture and we reject all the batches made in the facility since we had the bad result - this has happened in my experience but not very often and only when the contamination has been in Grade A areas. If we had instantaneous results we could test and approve a facility for sterile manufacture before starting up and



never lose a batch but we would be interrupting the production scheduling by doing that.

But let's look at this closely, what would we actually do if an environmental monitoring location in sterile manufacture was found to be out of specification and our system was that we were monitoring the area to approve it before start up? The least we could do would be to clean up the specific location, re-examine it and on the basis of the re-examination let production go ahead. The most we could do would be to demand that the whole area was re-cleaned, re-disinfected and re-monitored before production would be allowed to start up. There are obviously other options in between. Some people argue that the introduction of seat belts in cars has led to a decline in the standard of driving because there is a lower chance of being killed or seriously injured if you're wearing a seat belt. Is it necessarily going to lead to better standards of hygiene in manufacture if we get instantaneous results - I'm not so sure but I am prepared to believe that we could have a case for rapid methods here, but they really would have to be hyper-sensitive and genuinely instantaneous.

#### And finally...

Non-destructive testing. If speed of obtaining results is of no great advantage to improving the things that we are doing today, what should we be doing other than improving manufacturing control and promoting parametric release? I think the best direction is towards non-destructive testing to the point where we could either inspect every unit or apply statistical sampling techniques to give us a quantifiable assurance of our microbiological quality. The big restriction on our knowledge of the microbiology of our products is that once we've tested a product unit it becomes unsale-able - but we could get away from this with non-destructive testing.

I really don't know what commercial interest there is out there on the subject of non-destructive microbiological testing, but at the risk of being thought facetious we can see an application of non-destructive chemical testing at our international airports which might conceivably be applicable or adaptable to the detection of microbiological contamination. The Drugs Enforcement Agencies have dogs checking our baggage for narcotics, the Security Service have dogs checking our baggage for explosives, when will the FDA have us having dogs checking our pharmaceutical products for microbiological contamination? Is this a daft idea or is it a daft idea? keep on streakin'

## chairmans review



With some justification we can claim that the year 2000 has been a very busy and momentous one in the young life of PharMIG.

The transition of the Group from a private society to an incorporated private limited company was achieved on August 22, 2000. That this key change in PharMIG's organisation went so smoothly is the result of very good planning, taking sound advice and a lot of "behind the scenes" hard work, especially by Poly Hajjieris and Bob Johnson. PharMIG will remain a non-profit making professional organisation whose activities will be funded by membership fees and charges made for meetings and the conference organised by the Group.

Activities of the Group now encompass a wide range of meetings, visits to various centres of interest, the specific work of a number of Action Groups, joint symposia, the newsletter, the WEB site and our annual conference. However, organising such a diverse range of activities does not happen by accident! It is the result of a lot of hard work and enthusiasm by a lot of people - those who serve on the Committee and the numerous Members of the Action Groups so ably co-ordinated and led by Hazel Sarosi.

Our conference held in Peterborough on November 9th and 10th, 2000 was a great success. The organisation of the conference was a brilliant example of teamwork by the Committee, each of whom played their part whether in debate, discussion groups, organising the table top exhibition, or general running of the conference.

July 2001 will herald PharMIG's 10th anniversary, you can be sure that the Committee, with your help and support, will celebrate this in fine style by building on our success and consolidating our position as a leading and increasingly well respected professional organisation. The first event in 2001 is the practical training course on cleaning and disinfection to be held at the University of Bath on 24th and 25th January 2001. Planning of other activities is also well advanced and the 10th anniversary Conference is to be held in Peterborough once again at around the middle of November 2001. The months and years ahead will present a host of challenges and opportunities for PharMIG, many of which will emerge from the way the pharmaceutical industry continues to develop, and many from the continually evolving regulatory scenario. There has never been greater interest in microbiological issues from the regulators which, increasingly, cover the "life cycle" of a pharmaceutical product from original research through product development and clinical trials to full scale manufacture.

Key challenges exist in refining and improving microbiological control and monitoring methods and the issues presented by the increasing activity of biotech companies. Pressures on cost reduction will continue and hence pharmaceutical microbiologists will not escape (nor should they!) the effects of the market place. The challenge will be to provide newer and more cost-effective means of control. PharMIG, with the help and support of all its Members will embrace such challenges with enthusiasm and use the meetings and other means of communication, including the WEB site, as a continuous forum for debate and exchange of views. In closing, I am sure I speak for all Committee Members in thanking you, the Members of PharMIG, for your continued help and support. Please take every opportunity to participate in some or all of our activities and together we can make 2001, our anniversary year, a truly memorable milestone in PharMIG's history. Finally, may I wish to you all a very happy Christmas and a successful and exciting New Year.

David I R Begg

## members view on stability testing

According to USP 23 <1151>;

"The term stability with respect to a drug dosage form, refers to the chemical and physical integrity of the dosage unit and when appropriate, the ability of the dosage unit to maintain protection against microbiological contamination."2

The draft Guidance for Industry - Stability Testing of Drug Substances and Drug Products recommends microbial limits testing to be performed on capsules.

It is known that certain physical methods of analysis often give us more accurate results than equivalent microbiological methods. With regards to microbiological contamination during stability testing the results of a microbial limits test over the shelf life of the product will depend on the initial bioburden of the product, (many non sterile solid dosage forms will have an initial bioburden of zero), and/or the challenge to the product from the surrounding environment. For many products the surrounding environment may be the inside of a blister pack with few micro organisms present.

The water activity of a product can help us to predict whether that product is susceptible to microbiological contamination based on the knowledge that the growth of most bacteria is reduced at an aw below 0.90. Yeast and moulds can grow at a much lower aw of above 0.70.3

The water activity (aw) of the Soft Elastic Gelatin (S.E.G) shell material after encapsulation and drying is lower than the minimum aw which will permit the growth of micro organisms.1

The dried shell is hygroscopic and will take up water when surrounding relative humidity is high. The majority of capsules are packaged in blister packs impervious to water and are consequently unaffected by relative humidity of the surrounding environment. Those which do take on water will show an increase in moisture in chemical stability testing. The dosage unit has sufficient integrity to keep moisture uptake to a minimum and consequently keep water activity low.

In the case of non sterile, non aqueous materials, stability testing may be limited to water activity and only when chemical testing demonstrates that the material gains moisture on storage. Formulations with aw of <0.7 need not be tested microbiologically.

Therefore it should be acceptable to the FDA that microbiology testing on stability may be decided upon water activity of the formulation.

References:

- 1 - R. G. Stevens - A Study to determine the water activity required to initiate growth of challenging Micro Organisms in Soft Elastic Gelatin Squares.
- 2 - USP 23 <1151>.
- 3 - J.J. Kabara, D. S. Orth - Preservative - Free and Self - Preserving Cosmetics and Drugs : Principles and Practice.

**Hazel Sarosi**  
**Sanofi-Synthelabo**

## *The rapid microbiologists.....*

*Microbiologists can be a put upon lot,  
We slave over autoclaves getting all hot,  
The smells are lovely and wholesome they say,  
Strange how, that others always run away!*

*Advice we offer to the production floor,  
With our swabs and air sampler we go to war,  
Our kit frequently comes from years ago.  
With budgets tight we keep our costs low.*

*We nurture and encourage our cultures to grow,  
Traditional methods can sometimes be slow,  
Rapid methods are now developing fast,  
Long lead times could be a thing of the past.*

*Results within 2 days a novelty for us,  
Test times that low are a real plus,  
Once we're slick with our testing and  
paperwork too,  
Careful Chemist's we'll be waiting for you!!!*

*Anon*

# Setting environmental alert and action limits

Paul Lovegrove-Saville GlaxoWellcome Beckenham  
and Mel Perry GlaxoWellcome Ulverston

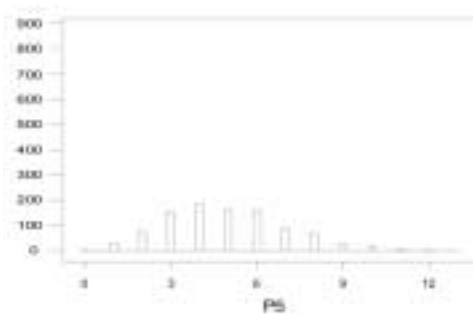
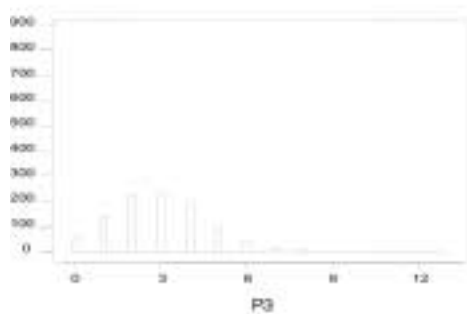
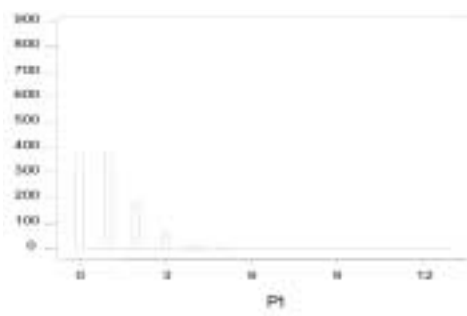
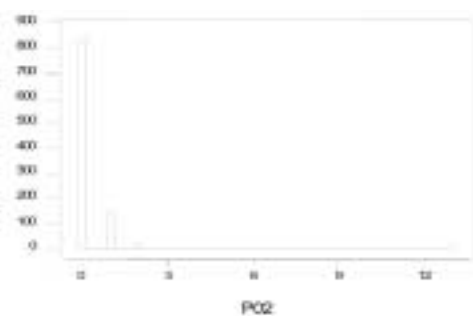
The setting of environmental alert and action limits is a much discussed topic. The focus is normally on comparing the different guidelines used in Europe such as the EC Guide to GMP and in North America where there are two main documents the FDA Guide to Aseptic processing and USP chapter 1116 part 1 to 3. The limits given in these documents are useful and the wise person will follow them to ensure that their manufacturing areas are controlled to the appropriate level to protect their products and to ensure successful regulatory inspections. Applying these guidance limits is not enough. Many microbiologists have found out the hard way by having the inspectors write the following observation; "Failed to base environmental monitoring limits on historic data". This still happens as I found when reading a recent issue of GMP Trends. USP Chapter 1116 talks about setting your limits based on historic data and that, limits should be reviewed at an appropriate established frequency. How historic environmental monitoring data is used in order to set limits is the topic of this article.

Alert and action levels are distinct from process parameters and product specifications in that they are used for monitoring and control rather than accept and reject decisions. Exceeding an alert or action level does not imply that product quality has been compromised. The purpose of alert and action levels for microbial samples is to enable environmental monitoring counts above the normal trend to be identified and appropriate action taken.

When setting limits the first priority is to ensure they are set at the right level to protect a particular process and where appropriate comply with the regulatory guidelines. The alert and action levels set may need to be lower than the level to protect the process to allow trends to be identified and to trigger actions when counts are above the normal level found. This is what your historic data is used for.

The method for setting the alert and action levels will depend on the type of distribution given by the counts. Distributions obtained from sterile areas will differ from non-sterile areas. This can be observed by producing histograms/charts of the microbial results. Its possible to test your data to determine the type of distribution you have but this may not always be necessary or practical. You will be looking for a best fit rather than a perfect model so it may not be relevant to carry out tests for the type of distribution.

The results from sterile areas tend to have a distribution close to a Poisson distribution. A Poisson distribution can be described as skewed, which will occur if your counts have a lot of zero's and you only occasionally have a sample with any colonies. The following histograms show how the Poisson distribution changes shape as the mean increases. With a mean of 0.2 cfu's the distribution has mainly zero counts with a few at 2 cfu's. When the mean is 1 cfu, most counts are either zero or one, but some counts up to 5 are observed. With a mean of 3 cfu's the number of counts spans 0 to 8 but the distribution is still skewed. Finally, with a mean of 5 cfu's the distribution is nearly symmetrical and can be adequately approximated by the normal distribution.



Y axis = frequency

X axis = number of samples



If a Poisson is observed, the alert and action levels are set at the 95th percentile and 99th percentile respectively. The values representing the percentiles can be looked up in statistical tables for the Poisson distribution with the same mean as that observed.

Results from areas which are non-sterile but environmentally controlled may yield distributions approximate to a Normal distribution. Such non-sterile areas would have levels set at +2 and +3 standard deviations from the mean for alert and action levels respectively. Environmental monitoring levels for these samples can be calculated by applying similar rationale to the method use for aseptic processing areas.

The 95th percentile is chosen to balance the risk of taking action when needed, against action when not needed, because the result may have arisen due to a random cause and not an assignable cause. When performing significance testing decisions are made at the 5% level as this is deemed a minimum decision criterion and implies that 1 time in 20 a wrong decision will be made. Similarly when stating the true location of the mean of a process, the 95% confidence interval implies the true value lies within this range 19 times in 20. A higher percentile, eg 97.5th percentile could be used for the alert limit. If this decision is taken it is more likely that the choice to take corrective action is right. In this instance a random count greater than the 97.5th percentile will occur 1 time in 40 observations. The choice between using the 95th or the 97.5th percentile is a balance in the risk of not taking action when action is required. Using the 95th percentile ensures more corrective actions are taken, but some of these will not have been necessary, ie a false alarm.

The Federal Standard 209E (FS 209E) for clean-room and clean-zones in controlled environments for airborne particulate cleanliness states that the upper level of confidence for each sample location is 95%. The FS 209E provides justification for using the levels of compliance of 95% and 99%. This allows for any samples above background level to be detected and the appropriate actions taken.

Use of the 95th percentile or +2 standard deviations from the mean for alert levels appears to be common

practice within our industry but 95th percentile may not be the best level for the reasons given above. If the data do not conform to a Poisson or Normal distribution, the percentiles of the observed distribution are used. The reason that the Poisson distribution does not fit the data is usually due to lack of control and thus non-randomness in the data. In many cases the data come from a mixture of Poisson distributions with changes in the mean level which create histograms with longer tails than expected.

Alert and actions levels based upon historic data can be set by producing frequency distributions of the numbers of colony forming units for each sample type within the clean room. Each sample type is taken separately i.e. settle plates exposed under laminar flow conditions (see table 1). Its possible to group samples from different process areas if the process activities are similar and the environmental monitoring results are within the same range.

It may prove valuable to remove outliers from the data sets as these can lead to inappropriately high alert/action levels. A method statement would be required for this purpose. The statistical method for removing outliers will depend on the type of distribution. However, some outliers may be removed due to knowledge that the sample was inadvertently contaminated by human borne colony forming species.

The percentage of samples for each level of colony forming units can then be calculated (see table 2). The cumulative frequency for each count category is given by the expression;

$$\frac{\sum_{r=0}^n f_r}{r_T} \times 100$$

The total number of samples is given by rT and the count for a particular category by rn. Thus, the sum of counts up to and including the category of interest is divided by the total counts and multiplied by 100 to give the current cumulative frequency. From table 2 you can select the best fit for your 95th and 99th percentile to give your alert and action level.

Table 1: Frequency Distribution of Environmental monitoring results

Sample Type	Number of samples with levels of colony forming units of:-										Total no. of samples
	0	1	2	3	4	5	6-10	11-15	16-20	21-40	
<b>Settle plates</b>											
Laminar Flow	1482	9	1	-----	1	-----	1	-----	-----	-----	1494
Bench	363	40	7	3	-----	-----	-----	-----	-----	-----	413
<b>Contact Plates</b>											
Laminar Flow	152	2	1	-----	-----	-----	-----	-----	-----	-----	155
Bench	43	2	-----	-----	-----	-----	-----	-----	-----	-----	45
Floor	32	9	4	-----	-----	-----	-----	-----	-----	-----	45
Changing Room	22	7	2	6	2	1	3	3	2	1	49
<b>Air Counts</b>											
Laminar Flow	95	-----	1	-----	1	-----	-----	-----	-----	-----	97
Bench	38	5	7	1	2	-----	-----	-----	-----	-----	53
Changing Room	33	-----	-----	-----	-----	-----	-----	-----	-----	1	34



The number of observations required for reliable limits depends on the method of setting the limits.

If the Poisson distribution can be shown to fit the data, a good model can be obtained from as few as thirty observations. However, if the limits are based on the historical data as a frequency distribution, many more observations are required. This is because with a few observations each observation provides a large step between count categories. As an example the air samples from the changing rooms (tables 1 and 2) show any count is an alert and the highest count the action limit, thus there is no gradation in the data. Ideally, many observations are required with 1000 or more preferred.

Once the limits have been set they need to be maintained. This can form part of the annual review

of the room monitoring data, with a formal limit revision exercise perhaps every three years. Of course if any engineering changes are made the review should be carried out soon after the change. The review simply consists of calculating the actual frequency of alerts and actions against the expected frequency of 95 and 99.9% respectively. If the frequency is much higher, either the limits are too strict or there are inadequacies in room cleanliness. Once the cause is established appropriate action can be taken which may be a revision of the limits.

Making limits more stringent is normally easy to justify but its important to be aware that counts go up as well as down. Higher counts may not mean that the product is at risk or that controls are not being effective they could result from increased production activity.

Table 2: The percentage of environmental monitoring samples with counts ≤ each frequency of occurrence.

% Compliance of samples for specific levels of colony forming units										
Sample Type	0	1	2	3	4	5	6 - 10	11-15	16-20	21-40
<b>Settle plates</b>										
Laminar Flow	99.2	99.8	99.9	-----	99.9	-----	100	-----	-----	-----
Bench	87.9	97.6	99.3	100	-----	-----	-----	-----	-----	-----
<b>Contact Plates</b>										
Laminar Flow	98.1	99.3	100	-----	-----	-----	-----	-----	-----	-----
Bench	95.5	100	-----	-----	-----	-----	-----	-----	-----	-----
Floor	71.1	91.1	100	-----	-----	-----	-----	-----	-----	-----
Changing Room	44.9	59.2	63.3	75.5	79.6	81.6	87.75	93.9	98.0	100
<b>Air Counts</b>										
Laminar Flow	97.9	-----	99.0	-----	100	-----	-----	-----	-----	-----
Bench	71.7	81.1	94.3	96.2	100	-----	-----	-----	-----	-----
Changing Room	97.1	-----	-----	-----	-----	-----	-----	-----	-----	100

## editors note

This time last year I wasn't on the PharMIG Committee or Editor of this newsletter but the pressure had started to build for me to get involved. My thoughts were; why me, leave me alone, I have enough to do, I don't want any more responsibility. Then January came and I found myself spending the weekend in the un-flooded city of York with the potential new PharMIG Committee and their families. I new I was walking into a trap and their cunning plan worked. After getting up at 5:00am to drive to York my wits were fuddled and I agreed to taken on the role of Editor. It was a good weekend, there was fun as well as work, David provided some quality wine with dinner and I felt I detected a new spirit and energy that would take PharMIG forward and allow the Committee to support each other. I left this meeting feeling in part flattered but also thinking O'God what have I done. It's true that in the past I had produced 3 newsletters for PharMIG, but pressure of work PAI's etc.. stopped me from carrying on with this work and I felt I had let people down. I was worried but as with most of life, your worries are unfounded. The first newsletter came together with little difficulty, just a steep learning curve with MS Publisher. The printing was poor but free and there are now good copies available if you want them. With the quality of this newsletter and the last one and being aware of articles that will be available in the future, I feel confident that it is sustainable. This is possible because of the quality of the people in the Committee and organisation as a whole. Thank you to everyone who has supported and helped with the newsletter in particular Poly Hajjipieris, Hazel Sarosi and Tim Sandle. I write in this vein, as it's the time of year to reflect. What can I say, other than, it's been good. The things that most Members see like the newsletter, meetings and conference have been very professional and well received. In the background a lot of good work has been performed in setting the foundations for PharMIG to move into a new era with its 10th year looming. And so to the future. Please keep writing and supporting PharMIG and if you can supply a picture or two with articles it would be great.



The pressures of work are still here for us all, so why bother ? because it's worth it.

Happy Christmas and New Year.

Paul Lovegrove-Saville



# PharMIG Action Group Update



Hazel Sarosi  
Action Group Co-ordinator

With the millennium year drawing to an end we have all noted many changes both within the Pharmaceutical Industry and within PharMIG. Harmonisation of the Bacterial Endotoxin Testing method has meant that we have all revisited our testing methods to ensure our continued compliance with the Pharmacopoeias. The Microbial Limits chapter has recently been issued for comment and has ironed out many of the idiosyncrasies that existed between the US and Europe. The Action Groups have also had a very interesting year and three in particular have achieved tremendous results when one considers that each Member also has significant responsibilities within their own organisations.

The Bacterial Endotoxin Action Group have recently compiled their first survey which you should all receive soon. I know that the group have carefully deliberated over some of the harmonisation issues and common BET problems. It is their intention to produce an updated guidance document as an addition to the official compendia testing requirements. They plan to propose

strategies for the testing of raw materials and excipients, to develop guidance on how to set limits as well as address other issues such as rounding policies. You will all have received a survey from the Biological Indicator Action Group recently which I hope you took a few moments of your time to complete. The response was 22 completed survey out of approximately 55 sent out. A big thank you to all those of you who did respond. The completed questionnaires have been analysed by the Action Group and the summary of results are included in this newsletter. Use them to benchmark yourselves within industry in an area where it is sometimes perceived that even the regulators have difficulty in forming a clear and consistent opinion.

The third particularly active Group this year is the Disinfectant Action Group. This Group have recently posted their first questionnaire and will use the feedback in a similar way. I asked Trudy how things had gone with the Disinfectant Action Group during this first year. She replied, "*Things have gone really well. Our first meeting in June saw us put together the Action Group Objectives for 2000 and compile questions for the disinfectant survey. Members have probably already received a copy of the questionnaire and I hope that they will be busy filling it in! The Group was also heavily involved in providing the content for the forthcoming 'Practical Training on Cleaning and Disinfection' course to be held at Bath University in January 2001. Finally, I'd like to say a big thank –you to all the Group Members for their participation and input to the PharMIG Members for challenging the Group (keep it up) and to the PharMIG Committee, and finally, thanks to Sue (my boss) for her help and support.*"



Trudy Adjrah  
Disinfectant Group Leader.

With the new PharMIG organisation and the commitment we have seen this year from all the Action Groups I am very confident that 2001 will be the year when PharMIG offer the members more than ever before. Finally, please remember that questionnaires are the starting point for all Action Groups and without your feedback, we do not know what your requirements or expectations are. Please use PharMIG to its full potential and make a new years resolution that you will complete every survey received. If there is anything that you would like to get out of us then please drop us a line. Remember, you can get in touch with any of the Committee through the website and we would all really love to hear from you!

Hazel Sarosi  
Action Group Co-ordinator



# Practical Training on Cleaning and Disinfection

## Programme Wednesday 24th January

10:00 - 10:30 Tea/Coffee and Registration

### Disinfection Theory:

A question of semantics  
Disinfectants types and modes of activity  
Factors affecting activity  
Mechanisms of resistance

### Industrial Guidelines and Practices:

Contamination control in sterile and non-sterile product areas  
Survey of current practices  
Cleaning in place  
Cleaning challenges  
Residues

### Lunch BREAK

### Practical Demonstration and Laboratory Work:

Good cleaning practice in clean rooms and non-sterile areas covering:

- Selection of agents, preparation, filtering, storage and dilution
- Compatibility and rotation of solutions
- Cleaning techniques
- SOP's, records and other documentation
- Handwashing techniques, surface and personnel monitoring
- Demonstration of EN1276 and surface tests

### Tea/Coffee BREAK

### Biological Decontamination of Controlled Environments - Isolators and Cleanrooms:

Gassing systems  
Cycle development, performance qualification, biological indicators  
Operating control factors  
Surface decontamination  
Directives and guidelines

Drinks and Dinner in Wessex House

## Programme Thursday 25th January

### Role of Environmental Monitoring in Contamination Control:

Development of a monitoring programme  
Monitoring methods: traditional vs. rapid  
Microbiological standards: sterile vs. non-sterile product areas  
Discussion of environmental monitoring results from previous day

### Tea/coffee BREAK

### Case studies:

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

### Validation - Regulatory Expectations:

Structure of a validation study

Documentary evidence and acceptance criteria

Sampling and analytical methods

Annex 15 and FDA guidance on validation of cleaning processes

### Lunch BREAK

### 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.**

*Please note that PharMIG reserves the right to alter the programme in the event of unforeseen circumstances.*

## PharMIG is now Limited - finally!

Finally received the certificate from Companies House to say that PharMIG is now registered - see the official wording from the certificate below. Our thanks goes to Robert Evans from the NCVO for his advice and support on this matter - a very efficient Legal Advisor! Guess we'd better pay settle his bill now! We have published an edited version of the documents sent to Companies house (equivalent to the old Terms of Reference) and copies were available at the conference, but will be sent out to all Members next month.

**'The Registrar of Companies for England and Wales hereby certifies that THE PHARMACEUTICAL INTEREST GROUP (PharMIG) is this day incorporated and that the Company is Limited' Company No. 4058017 22nd August 2000.**



# Results of The PharMIG Survey on Biological Indicators

PharMIG Steam Sterilisation Action Group Members

Natasha Gibbs	(GlaxoWellcome R&D)	Paul Newby	(GlaxoWellcome Ops)
Mark Asquith	(AstraZeneca)	Tom Norton	(GlaxoWellcome Ops)
Judith Boothman	(AstraZeneca)	Hester Pearson	(Boots)
Sheila Lawson	(Sanofi-Synthelabo)	Beverley Stout	(GlaxoWellcome Ops)
Emma McNeely	(GlaxoWellcome R&D)		

## INTRODUCTION

Through the Pharmaceutical Microbiology Interest Group (PharMIG) conference in November 1999 it became apparent there are still many issues on the validation of autoclaves that Members have concerns about. In particular the biovalidation of Steam sterilisers. The Action Group was put together with Members from 5 companies to try and address the issues with the help of PharMIG Members.

A questionnaire was distributed to all PharMIG Members and this document is a collation of the 22 replies. This questionnaire has started off the Steam Sterilisation Action Group; we have already prepared another questionnaire to be sent out soon, on Steam sterilisation. I hope that the response will be as good, as for this questionnaire. The combination of the two questionnaires will provide us with invaluable information for our monograph.

The aim of the Group is to act on behalf of PharMIG concerning any issues that members have on Steam sterilisation. If you have any issues that you would like to raise or queries on the questionnaires then please email on: [nsg68034@glaxowellcome.co.uk](mailto:nsg68034@glaxowellcome.co.uk).

**Natasha Gibbs**  
(Action Group Leader)

## Introductory Questions

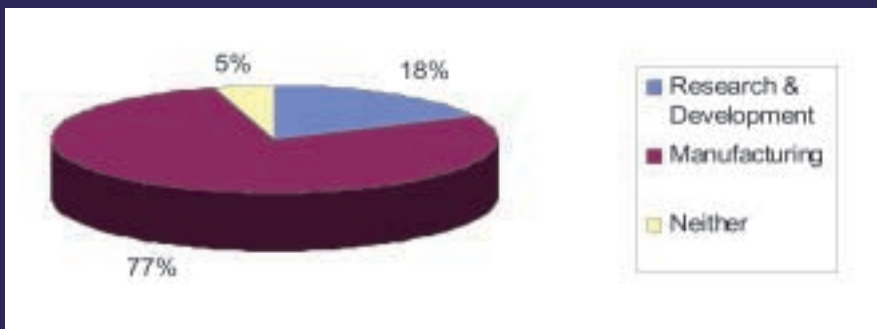
**Please give the industry for which you work:**

All respondents were Microbiologists who worked within the Pharmaceutical Industry with 2 respondents working in both the Pharmaceutical and Contract business.

**Please state the site at which you work:**

Research and Development	Manufacturing	Neither
4	17	1

## Site of Employment



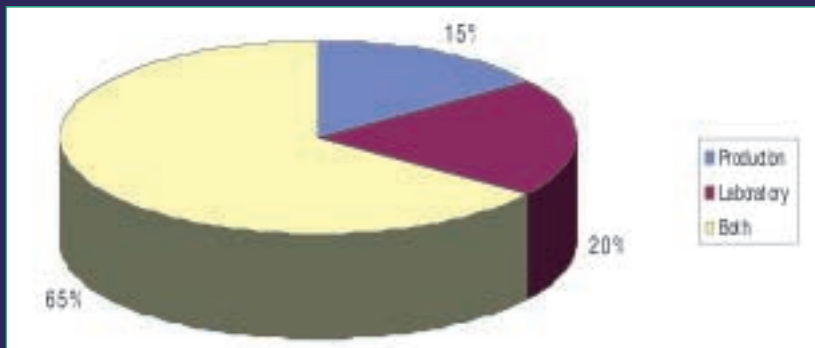
77% of the replies worked at a manufacturing site and 18% worked in R & D. The 5% who worked in neither worked for a packaging firm and a Quality control laboratory.



**What are the autoclaves used for?**

Production	Laboratory	Both
3	4	13

**What are the autoclaves used for?**

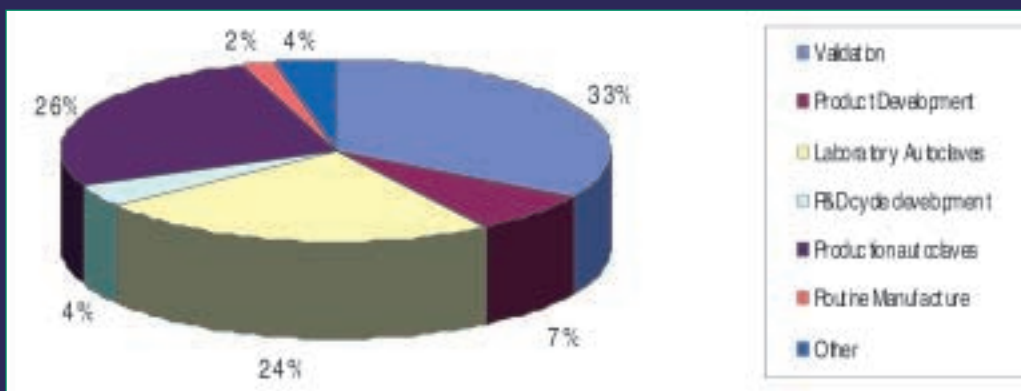


65% of the respondents used their autoclaves for both Production and Laboratory. Others had only Production autoclaves (15%) or laboratory autoclaves (20%).

**What do you use Biological Indicators for?**

Validation	Product Development	Laboratory Autoclaves	R&D Cycle Development	Production Autoclaves	Routine Manufacture	Other
18	4	13	2	14	1	2

**Use of Biological Indicators**



This pie chart shows the extent of use of BI's by those who responded

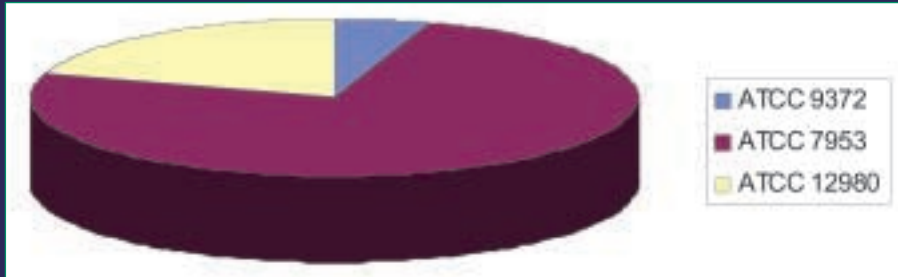


### What specific Biological Indicator do you use?

All replied *Bacillus stearothermophilis*.

ATCC 9372	ATCC 7953	ATCC 12980
1	15	4

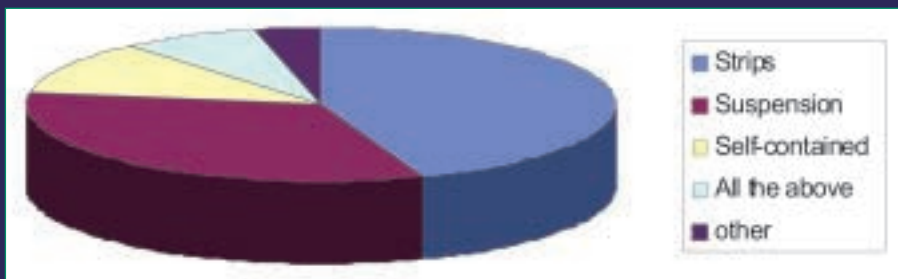
### The Strains of *Bacillus stearothermophilis* used



### What presentation of Biological Indicator do you use?

Strips	Suspension	Self-contained	All of the above
12	9	3	2

### Presentation of Biological Indicator used



Do you verify your spore suspension label claim?

YES	NO
57%	33%

57% of those who replied said they verified the spore suspension label claim.

### Of those who said yes, they performed those tests as follows:

Pour Plate	Surface Inoculation	Unknown
9	4	1

### Method for verifying the spore suspension label claim



YES	NO
57%	33%

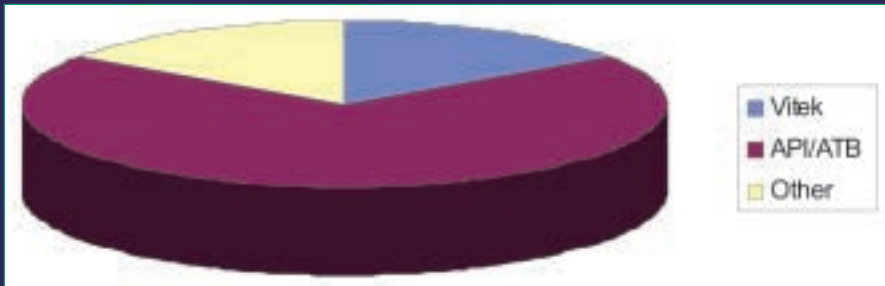
### Do you confirm the identity of your Biological Indicator?



### Which method do you use?

Vitek	API/ATB	*Other
2	9	2

### Biological Indicator identification methods

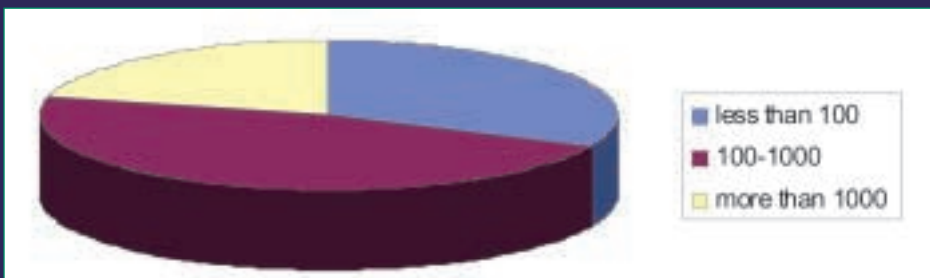


\*Other = Beckton Dickinson ID strips and Manual/Microscopes

### How many Biological Indicators per year do you use?

Less than 100	100-1000	More than 1000
6	9	4

### The Number of Biological Indicators used per year



### How often do you use Biological Indicators?

Daily	Weekly	Monthly	Annually	Randomly
1	4	3	10	1

### The Frequency of use of Biological Indicators



### What D-Value range do you usually use?

< 1.5	1.5 – 3.0	> 3	N/A	No Response
0	14	3	1	3

### D-Value range



### Do you calculate D-Values?

YES	NO
5	14

Of the 5 respondents who calculated D-Values, 4 use SMC and 1 uses linear regression to perform the calculation.

Of the 5 respondents who calculate D-Values, 3 verify the D value of each batch prior to use.

### Do you verify D-Values against any of the following substrates?

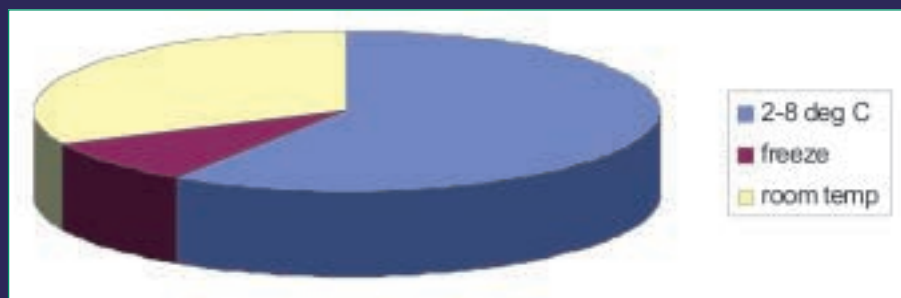
- Glass
- Paper
- Steel
- Water
- Rubber
- Product

Of the 5 who calculated D-Value, only 4 verify it against any of the above substrates.

### What are your BI storage conditions?

2-8°C	Freezing	Room Temperature
13	2	7

### BI Storage Conditions



There have been 5 respondents who have confirmed seeing an increase in D-Values.



# Suppliers

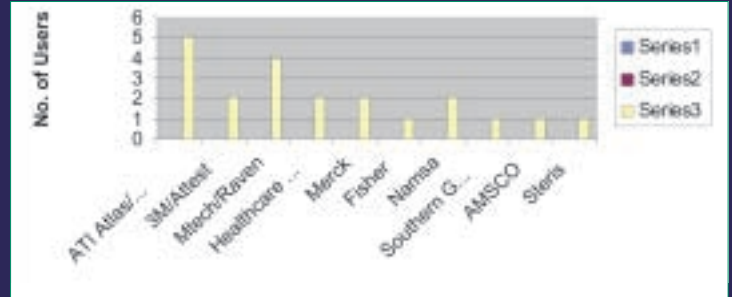
For spore suppliers, do you use commercial suppliers or manufacture in house?

All respondents use a commercial supplier.

Which suppliers do you use?

AT / Atlas / SGM BIOTECH	5
3M / Attest	2
Mtech / Raven	4
Healthcare Sciences	2
Merck	2
Fisher	1
Namsa	2
Southern Group Laboratories	1
AMSCO	1
Steris	1

Bi Suppliers



Have you audited your supplier?

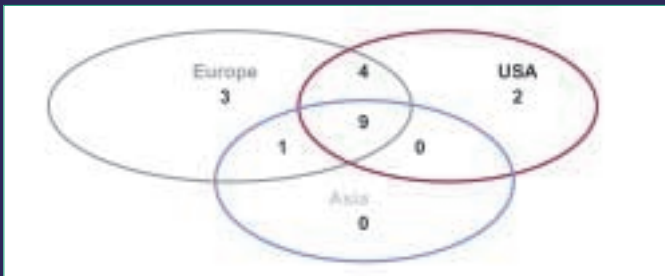
YES	NO
4	15

Are they on an "approved supplier" list?

YES	NO	No Response
6	9	4

# Regulatory

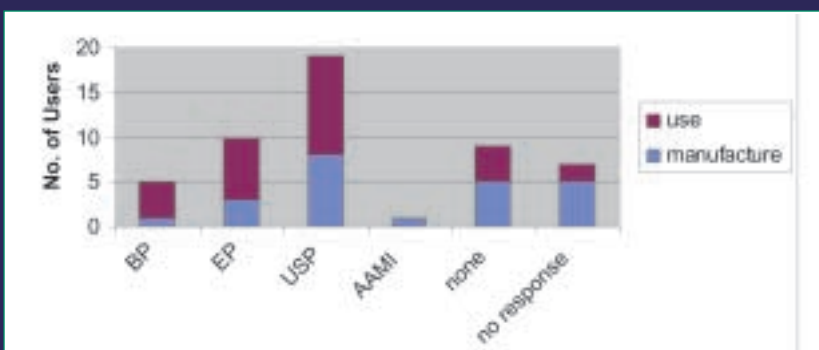
Where are your products marketed?



What regulatory documents do you apply to your process?

	BP	EP	USP	AAMI	None	No Response
Manufacture	1	3	8	1	5	5
Use	4	7	11	0	4	2

Regulatory documents



# Patsy Petri-Dish's problem page for Microbiologists.

*Dear Patsy Petri-Dish,*

*I am a new starter in a Microbiology lab and I'm finding it very difficult to control my pipetting. I have tried using different fingers and this seems to make no difference. Whenever I hold the pipette vertical the liquid drips out of the end.*  
*Sallie.*

Dear Sallie,

This is a common problem with new most lab personnel. I have a few tips that may help. Firstly always ensure that the end of your pipetting finger is dry, even a little moisture can make control more difficult. Most people use their index finger as this makes gripping the pipette with the other finger easier. My final tip is to have the end of the tip pressing against the part of your index finger where your finger print forms a swirl.  
Good luck with your lab career.  
Patsy.

*Dear Patsy Petri-Dish,*

*When carrying out preservative testing on creams using an Aspergillus culture I am finding it difficult to get the culture to mix in and distribute evenly. Do you have any suggestions that may help?*  
*Yours concerned of Hampshire.*

Dear Concerned,

Due to the nature of Aspergillus forming a homogenous solution is often a problem. Due to its colour it is easy to see the problem. Be aware you may be having this problem with other cultures but can't see them.

I have two suggestions that may help. You could try sterilising some glass beads and add a few to each cream; this really helps with the mixing of the solution. Alternatively use the end of a sterile loop to mix the solution and then break the loop off into the mixture.

I hope this helps,  
Patsy.

## diary dates

January 24th & 25th 2001 : Practical Training on Cleaning and Disinfection at The University of Bath. A two day workshop at the university campus to include lectures & practical demonstrations. Programme available from Poly at PharMIG. See page 9 for outline programme.

February 15th : PharMIG Visit to Celsis to look at Rapid Methods. Programme available early next year.

November 7th & 8th : The PharMIG Conference 2001

For further information, please telephone or fax Poly Hajipieris on: 01992-478675 or Email her on: [poly@pharmig.org.uk](mailto:poly@pharmig.org.uk)

## PharMIG

PO Box 117  
Broxbourne  
Herts  
EN10 7ZN  
Tel/Fax: 01992 478675  
email: [info@pharmig.org.uk](mailto:info@pharmig.org.uk)  
<http://www.pharmig.org.uk>



PharMIG 2000. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or any means electronically, mechanically, photocopied, recorded or otherwise, without prior permission and in writing from The Pharmaceutical Microbiology Interest Group (PharMIG). Please note that the views expressed by individual contributors and correspondents are their own and do not necessarily reflect the views of PharMIG as a whole.