

news



Chairman's Review

It is a great pleasure to report that PharMIG are the winners of the "Commitment to Training" award presented at the PCT 2002 Conference. The actual award was collected by Brian Alexander on behalf of the Group. Sadly the champagne which accompanied the award disappeared rather quickly!

This award is just one very tangible reflection of the quality and substance of PharMIG's efforts, and all the members involved in organizing and participating in our activities are to be congratulated.

The most recent, and very successful, event was the training course on disinfection, held at Bath University. Particular thanks, once again, must go to Roz Baird. Her unstinting efforts, together with other committee members, have established this course as an important annual event in the PharMIG programme.



Many of the members will know that Poly is now taking maternity leave and I am sure you will all want to join me in offering our best wishes for the forthcoming happy event. Meanwhile, our secretarial and admin. centre is being very efficiently organized and run by Gina Butti. Gina has previously worked in secretarial posts in the pharmaceutical industry and it is a pleasure to welcome her to PharMIG in Poly's absence.

Regulations or Guidelines? The membership, I am sure, must be well aware of the seemingly endless flood of regulations and somewhat euphemistically entitled guidelines that industry has had to cope with over the last 12 months. Some of these documents, in this writer's opinion, are unnecessary (e.g. Annex 15, Qualification and Validation) and extremely confusing (e.g. Annex 16, Batch Certification by the QP). Additionally, opportunities have been missed with the so-called EU consolidation directives 2001/83 and 82 to simplify and update.

The key objective of any new regulations and guidelines should be towards improved patient safety. Sadly, one is left wondering if the opposite effect is happening.

On the UK regulatory scene it has been announced that the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA) will be merged into a single executive agency of the Department of Health as from April 2003. A full text of the announcement appears elsewhere in this newsletter.

Finally, may I wish all PharMIG members and our supporters an enjoyable summer, be it in the UK, or on holiday in warmer climes. Haste ye all back to our forthcoming events!

David Beggs
Chairman, PharMIG

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The Potential Significance of Viable But Non Culturable (VBNC) Microorganisms in the Pharmaceutical Industry

by Paul Newby GSK

Introduction

Over the past 20 years a considerable body of evidence has been produced demonstrating the existence of metabolically active microorganisms in the environment incapable of being recovered using conventional microbiological methods. The term Viable But Not Culturable (VBNC) has been coined to describe such organisms. A lot of debate has focused on whether or not this VBNC state is, in fact, an artefact or reality. The existence of bacteria which exist in the VBNC state is now well established and documented (Colwell et al 1985, McDougald et al 1999) Much of the investigation work has centred on organisms from the natural environment, particularly aquatic organisms. Little information has been produced on the potential impact of VBNC organisms from industrial environments or processes. The potential impact on human health posed by VBNC organisms from industrial processes in the food, environmental and pharmaceutical sectors may be significant. VBNC organisms include pathogenic organisms which retain pathogenicity during the VBNC state. The situation is further complicated by the use of microbiological methods in these industries, incapable of recovery of VBNC organisms.

What is VBNC?

A bacterial cell can be described as Viable But Not Culturable (VBNC) if it fails to grow on recovery media normally suitable for that purpose yet retains metabolic activity and viability (Oliver 2000). Bacteria such as this are, in fact, in a state of dormancy.

A number of terms have been used to describe this physiological state including dormant, dead and somnambulant (Colwell, 2000). One such term used is 'somnia cell' (Roszak & Colwell 1987). The term 'nonculturable' was first derived from work carried out by Xu et al in 1982 (Xu et al 1982). Xu demonstrated that both *Escherichia coli* and *Vibrio cholerae* O1 demonstrated a survival or dormant stage when placed in a nutrient free environment. Xu showed that these cells remained metabolically active but were not recoverable using conventional culture methods. The term VBNC was developed by Colwell et al to describe microorganisms that do not form colonies on solid media but retained metabolic activity and viability (Colwell et al 1985)

VBNC is a survival strategy employed by a wide range of gram-negative heterotrophic bacteria and also by many nonsporulating gram-positive and gram-variable bacteria (see table 1). It appears to be a genetically inducible state (Oliver 2000). VBNC is an advantage to organisms living in changing environments such as the aquatic environment where sudden fluctuations in a range of conditions could potentially threaten survival. The ability to rapidly respond to changing conditions confers obvious evolutionary benefits. Environmental conditions seen to trigger the VBNC state include temperature, nutrient levels, salinity, age, oxygen levels and light levels. These factors are considered further in this text. The VBNC response to changes in environmental conditions is now being considered as a possible explanation as to why different species dominate the same location at different times of the year (Oliver 2000).

The Potential Significance of Viable But Non Culturable (VBNC) Microorganisms in the Pharmaceutical Industry

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Table 1 VBNC Bacteria

<p>Aeromonas salmonicida Agrobacterium tumefaciens Campylobacter jejuni Enterobacter aerogenes Enterococcus faecalis Escherichia coli Helicobacter pylori Klebsiella pneumoniae Lactobacillus plantarum Legionella pneumophila Micrococcus luteus M. varians Pasteurella piscida Pseudomonas aeruginosa P. fluorescens P. putida P. syringae Salmonella enteritidis S. typhimurium Shigella dysenteriae S. flexneri S. sonnei</p>	<p>Vibrio anguillarum V. campbellii V. cholerae V. fischeri V. Harveyi V. mimicus V. natriegens V. parahaemolyticus V. proteolytica V. vulnificus (biotypes 1 and 2)</p>
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VBNC associated morphological and physiological changes

Generally microorganisms showing enhanced capacity for survival in nutrient limiting environments show reduction in size and lower metabolic rates. In *Vibrio* spp this reduction in size has been described as 'rounding up'. Reduction in size from 2.27 to 2.14 μm for the enteric bacterium *Escherichia coli* has been described. In nutrient depleted aquatic environment microbial isolates have been shown to be smaller than in nutrient rich environments. Bacteria from seawater have been shown to be able of passing through 0.45 μm filters. Bacteria capable of passing through 0.2 μm filters have been termed 'ultramicrobacteria'. Responses such as these have considerable implications for pharmaceutical processes. Filters comprising of nominal pore sizes of 0.4 or 0.2 μm are routinely used as sterilising grade filters. Ultrabacteria aquatic organisms in the VBNC state with the capacity to pass through such filters could pose a threat to some pharmaceutical processes and could ultimately compromise the microbiological integrity of some product types.

Factors producing the VBNC state

A number of factors have been reported as being capable of producing the VBNC state in various bacteria. These include temperature, physiological age of the cell, nutritional status of the environment, oxygen light and salt levels.

Temperature has been reported as a significant factor for *Vibrio cholerae* (Xu 1982). VBNC state was induced by incubation temperatures of 4-6°C. The physiological age of *V. vulnificus* has been shown to have a significant effect on the VBNC status (Oliver et al, 1991). Logarithmic phase cells at 5°C entered the VBNC state in approximately half the time taken by stationary phase cells.

Nutrient levels have a profound effect on the VBNC status of microbial populations. Many investigations into the VBNC response have studied nutritionally low environments such as seawater, fresh water. Low oxygenation levels can reduce the time taken for cells of *C. jejuni* to enter the VBNC state.

Hypochlorite has been shown to induce the VBNC state in *Legionella pneumophila* (Bej et al 1991) and *Escherichia coli*. This observation has some significance to the pharmaceutical sector. Hypochlorite is widely used by the industry for its sporicidal properties. It is used to decontaminate plant and water systems. *Legionella* can be difficult to eradicate completely once a water system has been contaminated. Induction of a more resistant physiological state by an agent used to sanitise water systems may help partly to explain this recolonisation.

Methods of detection

Conventional microbiological culture methods using non-selective, selective, differential agars or broth enrichment are not suitable for the recovery of microorganisms in the VBNC state. Methods which are either currently used or which show potential include:

- Direct counting methods
- Dye reduction testes
- Immunological- based methods
- Genetic methods
- ATP bioluminescence
- Fluorescent labelling methods

For a more detailed outline of these techniques see the full text of this article in Newby 2001

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VBNC significance in the pharmaceutical sector Microbiological methods in the pharmaceutical sector are highly conservative. This conservatism coming as a result of the highly regulated nature of the industry. Agar plating methods, membrane filtration and broth enrichments are the main tools used for microbiological analysis of pharmaceutical input raw materials and finished products. These types of methods are wholly unsuitable for the recovery of organisms in the VBNC state. The significance, therefore, of VBNC organisms in the industry is subject to some debate. What is apparent, however, is that methods in the industry will need to change if a true assessment of the significance of such organisms is to be made. There is evidence that this is happening.

Areas of interest in pharmaceutical analysis include:

- Raw material testing
- Water analysis
- In-process bioburden testing
- Environmental monitoring
- Finished product testing

Microbiological control of pharmaceutical processes relies heavily on an understanding of process parameters. This understanding is obtained through process simulation trials, equipment validation, revalidation control and maintenance. Actual process control does not rely on actual microbiological monitoring, due to the time taken to produce results. Instead microbiological methods can only give assurance post manufacture that process controls and validated parameters have been maintained.

In addition, over time a picture is built up from trend data of the overall microbiological quality of the system. It is this high degree of control that ensures product quality is consistently maintained. However, as part of this process control it is important that the bioburden levels of input raw materials are accurately and sensitively monitored and understood. The data collected will demonstrate validation parameters of the process are being achieved and that over time the process is under control.

Deviations from trend data could be an early warning that changes are occurring which might result in some loss of process control. If input raw materials, particularly from natural sources, do contain organisms in the VBNC state then current methods of analysis are ill equipped to recover them. Water is a major input raw material of many pharmaceutical processes. VBNC organisms are widely found in the aquatic environment. This water is treated in various ways to reduce bioburden by filtration, distillation, heating, use of hypochlorite etc. all of which can induce the VBNC state in environmental microorganisms, some of which are pathogenic.

However, it is important that a true picture of the actual bioburden is obtained. Current methods may fail to give an accurate picture of total bioburden levels either because they lack sufficient sensitivity or worse are wholly unsuitable for the job. Failure to detect VBNC bacteria due

to inappropriate methodologies could therefore have potentially serious effects on pharmaceutical product quality.

A word of caution is required here. The potential for such an underestimate of actual bioburden levels in finished product is small. This is due to the massive overkill built in to many pharmaceutical processes. Also the aggressive nature of many manufacture processes will be highly antimicrobial. Examples of this include the widespread use of steam sterilisation, dry heat processing, sterilising grade filters and aseptic processing. Therefore, the real risk to patient safety from product contaminated with pathogenic organisms in the VBNC state must be considered small. The real risk posed by VBNC organisms to the pharmaceutical sector is in process understanding.

Accurate information must be generated on process and input raw materials. Failure to detect a significant portion of environmental microorganisms because of their morphological status must be considered in this context. Better understanding of the underlying microbiological picture through detection of VBNC organisms could have potentially far reaching consequences.

Use of new technologies with increased sensitivity and accuracy may profoundly change current bioburden limits, environmental methods and limits. Better characterised processes could even reduce the need for the sterility test in all sterile manufactured products.

Conclusions

Microbiologists have long recognised that there are significant numbers of microorganisms in the environment that cannot be cultured successfully with conventional methods. A wide range of nonsporulating Gram negative and Gram positive bacteria can exist in the Viable But Non Culturable state. The VBNC state can be regarded as a survival strategy conferring enhanced resistance to adverse conditions. Pathogenicity is maintained by some species during the VBNC state. As such these organisms could pose a potential threat to human health.

Introduction of new detection methods not requiring cell culture has raised the level of interest in VBNC organisms. The significance of such organisms is beginning to be considered. The full impact of VBNC bacteria on industrial processes has not been given consideration due in part to the widespread use of conventional culture methods incapable of detecting such organisms. There is an emergence of new methods and technologies in pharmaceutical microbiology and other sectors. These new methods have the potential of detecting VBNC organisms. Interest in the significance of such organism is growing and will continue to do so.

The true significance of VBNC organisms to the pharmaceutical industry is only just beginning to emerge. Alternative technologies may help play a role in significantly improving the quality of pharmaceutical products in the future. New methods of enumeration and identification with the potential for detecting VBNC organisms may bring about a radical reappraisal of bioburden limits, environmental monitoring techniques and limits. These methods could even drastically reduce the duration of the sterility test and could even remove the need for such a test due to improved process characterisation.

A greater understanding of VBNC organisms and their significance in pharmaceutical processes could therefore have profound effects on the way in which pharmaceutical microbiology is conducted in the future.

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Dear Reader

What can I say. England are out of the world cup but what a good run they had. It appears that they really captured the support of even the most die-hard non-football supporter like me. England should be happy that they did well although its always nice to win. However I am pleased to say that PharMIG won the Commitment to Training Award at the recent PCT Conference. Well done PharMIG.

This issue of PharMIG News has some interesting and thought provoking articles. Nigel Halls taking about Parametric release highlights some on the crazy things that we do in the name of compliance. How often have you had to justify your actions by saying that they are not based on science but compliance. The rules like many of our practices seem to evolve rather than being developed from clear scientific rationale. Take the use of local environmental wild types for media testing. It seems like a sensible idea that you should check that your environmental monitoring media will grow the organisms isolated in your processing areas. So we look at what's found and select some representative and frequently found isolates. As part of the process

the "wild types" are cultured helping them to adapt further to growth on media. And so we select isolates that we have a very good history of growing on our environmental monitoring media and then we culture them so that they are even better adapted. Well maybe I am stupid but I can not see any value in this but we are asked to do it. Wild types do have their place for example TSB used in media trials may not always grow *Micrococcus lutes*, which could cause you problems if its one of your commonly found isolates.

If you have anything, which bugs you, examples of compliance not science drop me a line make your view's known. Anonymously if you wish. It would be good to have a letter page in the PharMIG News or on the Web page where you can comment on articles and give your opinions but this will require you to write letters.

Paul Lovegrove-Saville
Glaxo Smith Kline

Would you be willing to host a Visit from PharMIG?

We are looking to build up a list of companies that are willing to host visits from PharMIG Members. The visits would last for one day and aim to provide PharMIG Members with an overview and better understanding of the wide range of work undertaken by other Members.

It is also an opportunity for information exchange and a way for Members to find out more about the work of PharMIG. If you are interested in taking part, please send your contact details to Gina Butti or Chris Randell at info@pharmig.org.uk <<mailto:info@pharmig.org.uk>> or tel: 01920 871999.

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Merger of Health Regulatory Agencies to strengthen Public Protection

The Medicines Control Agency (MCA) and the Medical Devices Agency (MDA) will be merged into a single executive agency from April 2003, announced Health Minister, Lord Philip Hunt, today.

The two agencies, responsible for the regulation of medicines and of medical devices, will combine to form a single agency responsible for both areas. The new agency will also have new arrangements for accountability and governance, with the addition of non-executive members to the agency board, and the establishment of a new post of Chairman.

The statutory basis for the regulation of both medicines and medical devices will remain as they currently are, and no legislative change is needed to bring about the merger. The systems and processes by which medicines are licensed and medical devices are controlled will not be affected.

Lord Philip Hunt said:

"The main reason for deciding in favour of merging the MCA and the MDA is the increasing convergence in the fields of pharmaceuticals and medical devices.

"As technology develops, there are likely to be growing numbers of products that cross the borderline between medicines and devices. For instance, some products are already a combination of drugs and devices. The boundaries will become even more blurred in the future. Through this change, the agency will be well placed to respond to the changing world of medicines and medical devices control.

"The two agencies operate under different legislation and make use of different sets of expert professionals. So although there will be some scope for integration of functions, our overriding aim will be to retain the highest possible standards of public health protection. The merger will have no effect on the legislation or regulatory processes that are tailored to each sector, and companies can be assured that they will continue to deal with an agency that is dedicated to the specific needs of their sector."

Ministers have also decided to introduce improved governance arrangements for the new agency when it is established. There will be non-executive members on the agency's board, and a new post of Chairman will be introduced. The Chairman will be an authoritative figurehead for the agency, able to represent the organisation and its decisions in public, as well as overseeing the board and the strategic management of the agency.

Philip Hunt continued:

"There will be considerable detail to be worked out in the coming months, and we will keep staff and stakeholders fully informed and involved as work progresses.

"The UK is renowned for its leading position in the regulation of medicines and of medical devices. Today's announcement represents a further step forward, which will benefit the management of these responsibilities and the protection of public health."

NOTES

1. The decision to merge the MCA and the MDA was announced today in response to a Parliamentary Question
2. Both organisations are executive agencies of the Department of Health, as will the new agency. No decision has yet been taken on the name of the combined agency.
3. The aim of the Medicines Control Agency is to safeguard public health by ensuring that all medicines on the UK market meet appropriate standards of safety, quality and efficacy. More information is at www.mca.gov.uk.
4. The Medical Devices Agency's responsibility is to help safeguard public health by working with users, manufacturers and legislators to ensure that medical devices meet appropriate standards of safety, quality and performance and that they comply with relevant directives of the European Union. More information is at www.medical-devices.gov.uk.
5. For media enquiries only, please contact David Daley in the Department of Health Media Centre on 020 7210 5656.



Parametric release – don't expect to get killed in the rush

Parametric release is a system of release based on information collected during the manufacturing process and also based on compliance with GMP. By and large it has come to mean release of sterile products without recourse to a pharmacopoeial Sterility Test.

As a professional microbiologist, parametric release has interested me pretty well since the day I first gave any thought to the pharmacopoeial Sterility Test – and that was probably on the first day I was introduced to the Sterility Test in the 1960's. I've always been a strong advocate of avoiding doing anything that smacks of giving little value from a lot of effort, and that describes the Sterility Test to a "T". Now with the publication of Annex 17 to the EU GMP Guide it's "all systems go" for parametric release! Or is it?

Let's look at what's happened with parametric release in the past to see if we can gauge what's going to happen in the future.

The Sterility Test first appeared in USP in the 1930's and in BP in the 1940's. Almost as soon as it was published it came under heavy critical fire. The basis of the criticism is well known.

- There are the statistics – if you had one non-sterile unit per 100 units (and no-one would risk marketing a sterile parenteral with that contamination frequency and expect to stay in business), you'd still manage to pass the Sterility Test of 20 units four out of every five times. This is patently absurd versus a standard of no more than one contaminated item in one million items.
- There are the media – it is a little paradoxical that the "media chosen for being suitable for recovering a wide range of microorganisms found in pharmaceutical manufacture" have been determined by decades of using these exact same media for environmental monitoring purposes to condition our expectations of what types of microorganisms are to be found in pharmaceutical manufacture.
- There is the cost – God knows how much money in capital costs (isolators, testing suites, air handling units, HEPA Filters etc), consumable costs (media, equipment, disinfectants, product samples etc) and labour costs is spent in the name of this practically value-less Test.
- There is the name - the Sterility Test. You'd expect with a name like this that the test was designed to confirm Sterility, certainly a lot of quite senior managers in the pharmaceutical industry evidently think so when microbiologists advocate sacking batches for

environmental reasons or autoclave failures. The Sterility Test does not confirm sterility. What it does is detect non-sterility. Basically if there is a "response" in the Test it means that the sample was non-sterile (or contaminated in testing), if there is no response it could well still mean there is a significant proportion of contaminated items in the batch.

- Finally there is the effect on the minds of professional pharmaceutical microbiologists – the demand for this wretched Test To be done, to be done quickly, to be done without contamination is a major diversion for the microbiologist away from where his/her focus ought to be – on contamination control and sterilisation in the manufacturing facility.

Now we have an Annex to the EU Guide which opens the door to getting rid of the Sterility Test as part of routine batch release, it maps out what we have to do to get regulatory approval for parametric release. But what's new? The pharmacopoeias have recognised the limitations of the Test for Sterility for years, they even include statements to that effect ("will pass, if tested") and specify clearly that it is intended to be a reference test in the even over a dispute over sterility – and surely the pharmacopoeias have a right to have such a test.

The pharmacopoeias have not been "blocking" parametric release. Nor indeed have the MCA. The opportunity to apply for permission to release terminally sterilised product without a routine batch by batch Sterility Test has been available for many years, and a small number of companies have been using parametric release for many years now. However, only a very few companies have ever applied, it is believed that most of those who have applied have succeeded in gaining permission but I am not aware of any statistics having been published.

So, if the Sterility Test is such a "duff" test and everyone's known it for decades, and the regulatory avenues for parametric release have not been closed (for terminally sterilised products at any rate); why have we not seen more real (as distinct from academic) interest? Many will argue, that the absence of clear guidance, such as that now given in Annex 17 is the reason. Certainly some of the EU Regulatory Agencies have been fighting shy of accepting applications over the past few years pending the publication of Annex 17 - and really you can't blame them, they don't want to create precedents which could end up with them getting "egg on their faces".

parametric release

At the heart of every company are the "bean counters". What are the financial advantages of parametric release ? They are pretty well as follows:

- Reduced inventory costs. But Annex 17 restricts parametric release to terminally sterilised products, for which the Test incubation period is only 7 days versus 14 days for aseptically filled sterile products. Unless terminally sterilised products comprise a major portion of a company's portfolio (as say with the LVP companies), the cost advantages of reduced inventories may be low.
- Reduced costs of batches rejected as result of "false failures". In reality these costs can never be high for a company that is surviving in sterile manufacture. Every Sterility Test failure has to be investigated and its long odds on the batch being eligible for repeat testing; the days of routinely allowed re-tests are long gone. This high profile given to failure has reduced the incidence of "false failures".
- Reduced laboratory overheads. How many companies are going to be able to decommission their Sterility Test laboratories by achieving parametric release ? Not many. Whether you are doing one Test per week or 50 tests per week your lab overheads remain the same.
- Reduced laboratory consumable and personnel costs. Chicken-feed compared to the rest of manufacturing costs.
- Improvements in the supply chain time from order placement to release and delivery. I don't know how to quantify this.

On the other hand what are the risks in the eyes of the "bean counters" ?

- The costs of initial regulatory approval. The cost of compiling and filing dossiers with the regulatory authorities, and responding to their queries is never insignificant.
- Increased cost of GMP Improvements and in-process controls where none was perceived necessary before, and/or its "evil twin" increased cost of having more batches rejected.

Let's look at the Guidance in detail to see if the "bean counters" might perceive that there might be more to lose than to gain from parametric release.

To gain approval to replace the Sterility Test by parametric release, Annex 17 requires that a risk analysis of the sterility assurance system should be done (3.7). The risk analysis should be focussed on an evaluation of releasing non-sterile products.

Explicitly there should be a system to control microbiological contamination in the product before

sterilisation (3.13). The Glossary to Annex 17 defines the sterility assurance system to include control of the starting materials, the environment and the manufacturing process. In other words the risk analysis (3.7) should generate approved specifications upon which decisions for release or rejection of a batch should be based for environmental monitoring data (3.17). Surely this means that batches will be expected to be rejected in the event of excursions beyond the specifications relating to microbiological environmental monitoring data and personnel monitoring data and (say) pressure differential lapses etc. And let's face reality - the regulators are not going to tolerate weak specifications in these areas to accommodate parametric release.

Those who go for parametric release are going to have to face the potential of batch rejection from excursions that precede a terminal sterilisation process which more than likely (eg if it were a PhEur overkill specification of 121°C for 15 minutes) would be sufficient to give a 10⁻⁶ SAL for far greater levels of contamination than could ever arise from such lapses.

Where this takes us is into the possibility of batch rejection and significant economic loss resulting from technician error in environmental monitoring, and technician and operator error in personnel monitoring and in the other detailed minutiae of environmental control.

Remember, that with the time lapse between date of microbiological environmental testing and date of results read-out, it is virtually impossible to invalidate a result. These unnecessary losses are factors which are directly parallel to those which the industry has spent a great deal of time and money engineering out of the Sterility Test by the now wide spread use of Sterility Test isolators.

I think that in the field of terminally sterilised small volume parenterals, an economic argument will prevail that there is potentially more to be lost from parametric release than there is to be gained. I don't think the MCA will be hiring legions of extra staff to vet parametric release applications. And in summary I think this is regrettable, because the Sterility Test adds little or nothing to our assurance of sterility, it distracts the focus of our microbiologists, and it may actually be an obstacle to real improvements in assuring sterility. What do you think ?

Nigel Halls

NHC-Nigel Halls Consulting
+44 (0) 1923 282828, mobile +44 (0) 7900 808670
nigelhalls@usa.net and nigelhalls@tiscali.co.uk

PharMIG won the Commitment to Training Award at the recent PCT Conference.

PharMIG Meetings Planner 2002

2002	Visit/Meeting/Course/Conference
June	
July	
August	
September	Proposed for early September - CABI Biosciences Micro Audit Meeting Surviving a Microbiological Audit
October	
November	Visit to Eli Lilly, Speke CONFERENCE 2002
December	Proposed for early December - Meeting at PQG Non-steriles

PharMIG Action Group

The Action Groups have continued to develop with there monograph sections.

The Non-Sterile monitoring Group issued their first questionnaire at the beginning of the year and I would like to thank all who have participated by providing there completed questionnaires. For those of you who have not received a questionnaire and would like to take part please contact myself and I will forward a copy onto you.



The Bacterial Endotoxin Group leader Lynne has been working with the Parenteral Society to see if there is the opportunity of collaboration with them to produce an industry standard monograph.

Trudy and her team on the Disinfectant Action group have met again in June, they been working hard on their sections for their monograph, which at this stage looks quite impressive.

There is also a new Group that will be forming to look at Water activity testing; the action group leader for this will be Sue Brewin from AstraZeneca. She is keen for this group to start and I would ask that if you would like to be part of this group that you contact myself.

I look forward to what the Action groups have to offer. The action groups are dynamic and do accept new members if you would like to know more information about the action groups or would like to participate in one then please contact myself on agc@pharmig.org.uk.

Natasha Gibbs

conference 2002

Wednesday 27th & Thursday 28th November 2002 Peterborough Moat House Hotel

This year's Conference puts the spotlight on both the general and specific aspects of Microbiological Quality Assurance in the pharmaceutical industry. In addition, the Conference will have a distinctly European flavour since we are fortunate to have the contributions of very eminent speakers from Holland and Switzerland, as well as those from the UK.

With the formal lectures, round table discussions and open discussion sessions PharMIG is also responding to a number of requests from members to provide some more detailed treatment of specific technical topics. However, this is not to lose sight of "big picture" issues where Microbiologists have an increasingly valuable role to play in supporting and managing Pharmaceutical Quality Assurance.

Potentially more difficult areas such as microbiological risk assessment and microbiological failure investigation, often the focus of attention for regulatory inspectors, will also be dealt with. Such issues inevitably call for fine judgement based upon sound practical experience and intuition.

Training is one of the current regulatory "hot spots" and an MCA view will challenge microbiologist's programmes on this topic.

Action group leaders will be playing a prominent role again, especially in the round table discussions.

As on previous occasions, the Conference offers a golden opportunity for Members to meet each other and to benefit from a wide range of topics covering microbiological QA. Of equal value is the time spent discussing common issues and concerns, exchanging ideas, networking and of course, having just a little time out enjoying the now traditional entertainment which is part of the PharMIG Conference.

TABLE-TOP EXHIBITION

As an integral part of the PharMIG Conference, there will be a tabletop exhibition at the Conference providing delegates with the opportunity to meet a wide range of suppliers and their technical representatives in a relaxed atmosphere. There are ample opportunities to view the displays, particularly in the evening of Wednesday 27th November.

THE VENUE

The Conference will be held at the Peterborough Moat House Hotel in Cambridgeshire. The hotel has excellent facilities including a modern leisure centre with swimming pool and fitness centre. Peterborough is exceptionally convenient for travel by rail (approx 1 hour from Kings Cross) and by road (A1M). A limited number of rooms have been reserved at a special rate for overnight delegates (so book early).

CONFERENCE FEES

Conference fees are detailed below and include lunches, Conference banquet, refreshments and Conference documentation. Conference fees do not include accommodation and if Bed & Breakfast is required for either 26/27th November you should book directly with the hotel at the special rate of £95.00. Cheques should be made payable to PharMIG and crossed A/C Payee only. Fees are in sterling and are VAT exempt.

Member Fees:	£ 495.00	Non Member Fees:	£ 645.00
Bed & Breakfast:	£ 95.00	Bed & Breakfast:	£ 95.00
(B&B to be booked directly with hotel)		(B&B to be booked directly with hotel)	

NB: Fees must be paid by 1st November 2002 in order to guarantee place(s) at the Conference.

REGISTRATION PROCESS

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

PROGRAMME WEDNESDAY 27TH NOVEMBER

Chairman	Mr David Begg* PharMIG Chairman
09:30 - 10:15	Tea/Coffee and Registration
10:15 - 10:30	Chairman's Welcome and Introduction
10:30 - 11:30	Key Note Lecture Current Challenges in Pharmaceutical Microbiological QA
SPEAKER 1:	Dr Werner Hecker, Novartis Pharma Stein AG, Switzerland
11:30 - 12:15	Non-Sterile Environmental Contamination Control
SPEAKER 2:	Mr Martin Lush, David Begg Associates
12:15 - 13:45	EXHIBITION with Finger Buffet Lunch Including Round Table Discussions Risk Assessment – Microbiological Issues
13:45 - 14:30	Mr Stewart Green, Wyeth Pharmaceuticals (UK)
SPEAKER 3:	EXHIBITION with Tea & Coffee
14:30 - 15:00	Microbial Failure Investigations Simplified!
15:00 - 16:00	Mrs T Jolanda Schoemaker, Crucell, Holland BV
SPEAKER 4:	Panel Discussion and Close
16:00 - 16:30	AGM (Members only)
16:30 - 17:30	~~~~~
18:45 - 20:00	Pre-dinner Reception in the EXHIBITION AREA
20:00 'til Late	Conference Dinner & Dance (Smart attire required)

PROGRAMME THURSDAY 28TH NOVEMBER

Chairman	Mr David Begg* PharMIG Chairman
09:00 - 09:15	Chairman's Remarks
09:15 - 10:00	Engineering Microbiological Improvement into Existing Operations
SPEAKER 5:	Mr Gordon Farquharson, Bovis Lend Lease Pharmaceuticals
10:00 - 11:15	Open Discussion (See overleaf) running concurrently
Sessions 1, 2, & 3	EXHIBITION with Tea & Coffee
11:15 - 11:45	Open Discussion (See overleaf) running concurrently
11:45 - 13:00	EXHIBITION & Buffet Lunch
Sessions 1, 2, & 3	Challenging your Microbial Training Programme
13:00 - 14:15	Mr Paul Hargreaves, MCA
14:15 - 15:00	Panel Discussion Session
SPEAKER 6:	Summary and Close of Conference
15:00 - 15:30	Tea/Coffee and Departure
15:30 - 15:45	
15:45 - 16:00	

*Honorary Member of PharMIG

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

Surviving a Microbiological Audit

PROGRAMME WEDNESDAY 18TH SEPTEMBER

09:30 to 10:00	Registration with Tea/Coffee
10:00 to 10:15	Chairperson's Welcome Mr Andy Martin
10:15 to 11:15	What an Auditor would expect to find in a Microbiological Audit Mrs Erika Notman
11:15 to 11:30	Tea/Coffee Break
11:30 to 12:30	Interactive Session A – Essential Behavioural Skills Mr Les Meader
12:30 to 13:45	LUNCH
13:45 to 14:45	Interactive Session B – Audit Scenarios and Discussions Mr Paul Lovegrove-Saville Mr Andy Martin
14:45 to 15:00	Tea/Coffee Break
15:00 to 15:45	Topical Issues in Pharmaceutical Microbiology Dr Robert Johnson
15:45 to 16:15	Panel Discussion with Speakers
16:15 to 16:30	Summary and Close

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

INTRODUCTION

PharMIG introduced this successful one-day meeting last year. This course has been tailored to some of the unique issues associated with a Pharmaceutical Microbiology audit. Many real life examples will be used and the meeting has been designed to encourage discussion.

At the end of the course, delegates should benefit from discussing their shared experiences and have a better understanding of how to avoid the pitfalls that exist when experiencing a microbiological audit.

PharMIG have introduced this one-day meeting for people working in the laboratory, microbiology & technical supervisors and managers, and other Quality professionals working in both manufacturing and research facilities. Delegates will gain an insight into the unique problems facing a regulatory audit with a microbiological emphasis.

Attendance will be limited to encourage discussion during the day. A certificate of attendance will be issued to the delegates for their training records.

THE VENUE

The meeting will take place at the De Vries Belmont Woods Hotel near Gwentham. It is a short drive from the A1 at Gonerby Moor and 60 minutes from Kings Cross station. This hotel has full conference facilities with accommodation, dining choices and a Leisure Club. Delegates staying overnight can take advantage of the Leisure Club facilities, which include a heated pool, sauna, steam room, squash, PGA approved golf course, hair and beauty studio.

For anyone wishing to arrive on the evening of Tuesday 17th September, a small number of rooms have been reserved at a special rate on a bed & breakfast basis of £109. Accommodation is an additional cost and must be booked directly with the hotel on Tel: 01476 993200; Fax: 01476 574547 or email: beltonwoods@delvries-hotels.com. As delegates may arrive at different times throughout the evening, arrangements for dinner should be made directly with the hotel prior to arrival.

COURSE FEES

Course fees are detailed below and include lunch, refreshments and course documentation.

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

Member Fees		Non Member Fees	
Day Delegate	£225.00	Day Delegate	£305.00
Bed & Breakfast	£109.00	Bed & Breakfast	£109.00

REGISTRATION PROCESS

Simply complete the attached reply card and return directly to the **PharMIG Administrator** with your payment or fax ahead your registration details to **01992 - 871166**. Places are limited and reserved on a **'First Come, First Served'** basis, so book early to avoid disappointment. All places will be held provisionally until full payment is received. Confirmation of an allocated space will be sent by post with travel directions.

CANCELLATION POLICY

Written cancellations will be accepted up to 30 days prior to the event, and all cancellations will incur a fee. No refunds are available for cancellations 15 working days before the start date and full course fees will be due for delegates who fail to attend. Substitutions may be made at any time, preferably in writing to the Administrator.

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