

PharMIG

The Pharmaceutical Microbiology Interest Group

News

Issue 6 October 2001



Don't miss Conference 2001

PharMIG 10th Anniversary celebration

Pharmaceutical Microbiology - Vision for the Future

Wednesday 7th & Thursday 8th November 2001 - see inside for details

chairman's review



As I write this short review our 10th Anniversary Conference is exactly 4 weeks away!

It seems almost like yesterday that we sat down and planned the event. Much hard work has been put in by the Committee (and the speakers!) to make this our best event ever. All our plans are complete and in place – all we need now is you the delegates.

However, this review is not just an exhortation for you to attend the Conference because I am sure, by now, you are fully aware of the excellent programme of lectures, open discussion sessions and the exhibition. What is also very important to note is the fact that under our new constitution as PharMIG Ltd we are obliged to hold the **First Annual General Meeting**. This will take place on **Wednesday 7th November 2001** from 16.30 until 17.30.

Under the new rules all the Committee Members will stand down and may seek re-election should they wish. Therefore, I am hopeful that many of the Members will also put themselves forward for the various Committee positions. In my view it is vital that we have "new blood" to help in steering PharMIG into the next decade. Succession planning, I believe, must be a key element in our strategy. So come on, put your nominations forward for election!

Another important part of the AGM is your opportunity to comment and question the manner in which PharMIG is operated. Your questions, comments and ideas are very important. The Committee can do their best to run PharMIG for the benefit of the Members, but Members own comments and ideas are paramount in ensuring that the Committee remain in touch and that we stay loyal to our core values. So please come to the AGM and have your say! If by chance you cannot make the Conference and the AGM please do not hesitate to write to myself or any of the Committee offering comments, asking questions, or putting forward ideas for consideration.

Finally, for those coming to our Conference I offer a very warm welcome and look forward to meeting and talking with as many Members as possible.

David I R Begg
Chairman PharMIG

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surviving a microbiological audit



The first PharMIG training day dedicated to 'Surviving A Microbiological Audit' took place on 26th September in the sprawling elegance of Belton Woods Hotel in Lincolnshire. The attendee list contained the usual array of differing backgrounds and personal experiences. However, everyone was united in aspiring to achieve a common objective – to learn and inwardly digest as much information as possible about how to prepare, deal with, and survive a microbiological audit.

T. H. Huxley, a 19th century English biologist once remarked: "The great tragedy of Science is the slaying of a beautiful hypothesis by an ugly fact". Whilst many aspects of microbiological work could relate to this assertion, it is during an audit, whether it be internal, MCA, FDA or other, when those 'ugly facts' tragically conspire to raise their ugly heads at the most cursingly inopportune moments!

Achieving standards demanded by audits and auditors is an innate part of our industry, but training in how to prepare, react and positively survive an audit is not always consistent or even accessible. The four seminars presented at this meeting set out to provide the attendees with an appropriate standard of knowledge and industry intelligence on the audit process and, perhaps equally as important, the tactics used covertly and overtly by an increasing number of auditors to extract the desired information.

The first seminar was by Erika Notman (Boots Healthcare International) and was an insight into what a microbiological audit might consist of. Serving as a refresher for the more experienced and a comprehensive introduction for the more unfamiliar, this seminar laid the foundation on which the rest of the day was built. Fundamentals on how and why audits are performed and by whom were interlaced with stories from Erika's wide breadth of experience on specific audit scenarios which thrust the reality of an audit into the minds of all the attendees!

Following this was the double act of Paul Lovegrove – Saville (GSK) and Mary-Anne Weatherhead (Wyeth Manufacturing UK) who dealt with specific microbiological issues relevant to both aseptic and non-sterile processing. This interactive session unleashed prolific and lively discussion on various hot topics and contentious issues, including elements of environmental monitoring and WFI testing, which was only interrupted by the call to lunch! This was a useful session as the group was able to share opinions and concerns within a sympathetic forum.



The post lunch 'graveyard shift', as it was called, was taken by Les Meader (also from Wyeth Manufacturing UK) who, through his interactive seminar on essential behavioural skills, endeavoured to avoid the heavy eyelids and heavier stomachs typical at this time of day. This was achieved by inspired use of balloon blowing, body language and Bob The Builder! From this session attendees learnt about auditors' tactics for obtaining information as well as methods utilised by auditees in counteracting and disarming such tactics.

The last, but by no means least (in more ways than one!) was a session run by Bob Johnson (GSK) who provided a very comprehensive, thought provoking and invaluable list of contemporary hot topics collected through collation and analysis of FDA 483s or warning letters and audit feedback by other regulatory bodies. Through over 50 individual slides Bob provided a potted history of significant non-compliances on an international scale from the end of the last decade to present day. This information is without doubt additional armoury in the fight for audit survival!

The day concluded as it had started – by providing each attendee with the necessary information and resolve to achieve the best out of their next audit. This was the first time that PharMIG had planned an entire day on the survival of a microbiological audit and the positive and enthusiastic response from the attendees was testimony to the well planned and delivered seminars. This training is invaluable for many members working within the microbiological field and beyond (we also welcomed into the fold some of our colleagues from analytical chemistry!)

At the end of what was commonly agreed to be a successful and constructive day, arguably the principal take-home message was: preparation, preparation, preparation! Within an industry where our working practices and standards are constantly and critically observed by the auditor, it is fitting for me to end this account with a second quote from a famous bacteriologist and chemist which is just as relevant today as it was a century ago:

"Where observation is concerned, chance favours the prepared mind." (Louis Pasteur, 1900)

Iain Bradbury – Microbiology Technician II, Bio Products Laboratory



diary dates

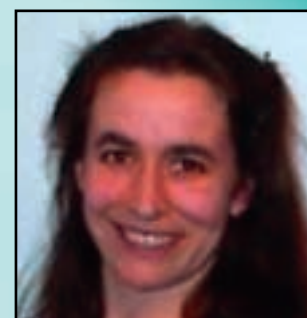
October 18th: Day Visit to La Calhene. A day of presentations on isolater technology covering design & disinfection and including a short tour of facilities. Lunch is included and kindly hosted by La Calhene at their site in St Ives, Cambridgeshire.

November 7th & 8th: PharMIG Conference 2001. The theme is: Pharmaceutical Microbiology – Vision for the Future. A 2 day event with an international list of speakers, AGM and tabletop exhibition.

10th & 11th April 2002: Practical Training on Cleaning & Disinfection at Bath University. A two day workshop at the University campus that will include lectures & practical demonstrations. Key lecturers will be Dr Roz Baird & Dr Anthony Smith. The programme currently in draft will be available by December 2001. For further information contact Poly Hajipieris on: 01992-478675 or Email: poly@pharmig .org.uk.

action group update

By now you should all be aware that this years conference is extra special for PharMIG members in that it is our 10th Anniversary. You will have all received a copy of the conference program and I think you will agree that it will prove to be an exceptional conference at the cutting edge of Pharmaceutical Microbiology.



I feel very privileged to have been given the opportunity to be involved with PharMIG at a committee level over the past year. I also feel very privileged to have had the opportunity to work with some very exceptional people- the Action Group members. There will be a short presentation at the 10th Anniversary Conference from 3 of the action groups. They will be giving you an update of activities so far and providing feedback on some of the survey results. I have found the dedication and diligence of the current action groups members quite overwhelming, especially at a time of so many mergers and heavy workloads. The compilation of the monographs are ongoing and the we are continuing to forge ahead utilising all areas of todays technologies. I participated in the last Disinfectants Action Groups meeting by teleconference last month which worked extremely well. Finally, I would just like you all to join me in congratulating Elaine Dymond (Disinfectants Action Group) who, at a time of many mergers, heavy workloads and Action Group participation, was successful in passing her QP viva since last issue. Congratulations Elaine!!!

Hazel Sarosi

Action Group Coordinator



editors note

Dear reader,

With the AGM fast approaching and the election of a new committee I thought I would take this opportunity to tell you what it's like to be a member of the PharMIG committee. It's absolute hell, tremendous pressure, lots of work and no reward. I think not. It's fun and satisfying. The committee supports each other and work well together.



For me each issue of the newsletter gives me considerable pleasure and the feed back about it make me feel that I have contributed to something worth while. How often do you feel that? This also applies to the action groups, courses and meetings whether I have been involved in them or not, as part of PharMIG I share in the success.

There are deadlines and work that has to be done but we try to share this so that it does not fall on one persons shoulders and we tend to cover for each other when necessary. Committee meetings cover important serious topics but are light hearted with cakes on the table to keep us going. The committee's time is also spent at the dinner table or in the bar where good wine oils the discussion. These sessions can be hard work but are rewarding.

Being on the committee is good for the individual in that you can gain new skills, it enhances your networking in the industry and can lead to the head hunters knocking on your door.

All in all it's a good crack and worth the effort. Thanks to everyone who helped me in my role and contributed to the newsletter. The newsletter only happens because you contribute and Poly helps me.

Paul Lovegrove-Saville

GlaxoSmithKline



Conference 2001

Wednesday 7th & Thursday 8th November 2001
Peterborough Moat House Hotel

Conference 2001 is a fitting venue to celebrate our 10th anniversary in fine style. The range of technical presentations will be given by an outstanding selection of international speakers. PharMIG is especially fortunate to have Dr Bob Morrissey from Johnson & Johnson in the USA as our special guest speaker. In addition, we are delighted to welcome back Dr Nigel Halls and Dr Peter Gilbert, both of whom are staunch supporters of our organisation. As usual, we can rely on Nigel and Peter to provide some incisive and thought provoking views! From the MCA we are pleased to welcome for the first time, Mr Andrew Bill who will guide us through the latest news on Parametric Release to be followed by hot debate in the Open Discussion Session led by Sharon Johnson. Our last speaker of the Conference, Dr Manish Parekh, has agreed to fly all the way from Chicago to enlighten us on bioprobes.

The Conference will provide the opportunity for the Action Group Leaders to present the results of their hard work.

The enthusiasm and energy of our Action Group Members has resulted in the compilation of some extremely valuable data and information across a range of subjects. The opportunity for the Membership to hear at first hand about the work of Action Groups is long overdue.

As on previous occasions, our Conference offers a golden opportunity for Members to meet each other and to benefit from a first class professional forum. Equally important is the time spent discussing common issues, exchanging ideas, networking and of course, having just a little time out enjoying the now traditional entertainment which is part of the PharMIG Conference.

To book a place or for further information, please contact Poly at PharMIG on 01992 478675 or poly@pharmig.org.uk

PROGRAMME WEDNESDAY 7TH NOVEMBER

09:30 - 10:15	Tea/Coffee and Registration
10:15 - 10:30	Chairman's Welcome and Introduction Mr. David Begg * ^C PharMIG Chairman
10:30 - 11:30	Key Note Lecture The Vision for Pharmaceutical Microbiologists SPEAKER 1: Dr. Robert F Morrissey
11:30 - 12:15	Cutting Edge Issues for Pharmaceutical Microbiologists SPEAKER 2: Dr. Nigel Halls
12:15 - 13:45	EXHIBITION & Finger Buffet Lunch
13:45 - 14:30	Molecular Microbiology: W(h)ither Physiology! SPEAKER 3: Dr. Peter Gilbert
14:30 - 15:00	EXHIBITION with Tea & Coffee
15:00 - 16:00	Action Group Reviews SPEAKERS 4,5 &6 (see over)
16:00 - 16:30	Panel Discussion and Close
16:30 - 17:30	AGM (Members only)
19:00 - 20:00	EXHIBITION including Pre-dinner Drinks and Canapés
20:00 'til Late	Conference Dinner & Dance (Smart Attire Required)

PROGRAMME THURSDAY 8TH NOVEMBER

09:00 - 09:15	Chairman's Remarks Mr. David Begg * ^C PharMIG Chairman
9:15 - 10:00	Parametric Release – Myth or Reality? SPEAKER 7: Mr. Andrew Bill
10:00 - 11:15	Open Discussion Session (See overleaf) Sessions 1, 2, & 3 running concurrently
11:15 - 11:45	EXHIBITION with Tea & Coffee
11:45 - 13:00	Open Discussion Session (See overleaf) Sessions 1, 2, & 3 running concurrently
13:00 - 14:15	EXHIBITION & Lunch
14:15 - 15:00	Rapid Methods in the 21st Century - Utilising Molecular Biology & Biochips SPEAKER 8: Dr. Manish Parekh
15:00 - 15:30	Open Discussion Session
15:30 - 15:45	Summary and Close of Conference



Management & Interpretation of Pharmaceutical Microbiological Data

21st June 2001, The Village Hotel, Nottingham, Chairperson: Hazel Sarosi

The inability of micro-organisms to behave themselves when tested does make interpretation of microbiological data more of a challenge. Organisms are only present in low numbers (hopefully!) and they don't tend to distribute evenly through the material being sampled. Coupled with the fact that the test method may or may not accurately count all cells present means that evaluation of the results is not as straight forward as one would like. However, a good understanding of the statistical principles and methods for meaningful interpretation of the data provide the microbiologist with the tools to do the job. With the correct approach to data analysis it is possible to get an accurate picture of what is happening in the manufacturing area or the suitability of method validation and product testing protocols. That was the objective of this workshop – to provide the basics on ways of managing and interpreting pharmaceutical microbiology data.

Statistics for the microbiologist

George Gettinby, Professor of Statistics and Modelling Science at University of Strathclyde, got the ball rolling with a crash course in statistics, control charts and experimental design. George started from the very beginning, i.e. frequency/probability plots and the statistical basis of why count plates should have 25 – 250 colonies per plate (data has Poisson distribution and the percentage error is between 6 and 20%; any lower counts and the percentage error increases.). The presentation then moved on to a quick overview of statistical process control (SPC) methods, explaining the need to understand the process and what happens if it goes wrong. For example, 80% of problems can be attributed to 20% of factors effecting the process (Pareto Rule), while Ishikawa diagrams can be used to identify cause and effect on a system. Also, a big influencing factor for maintaining quality processes is management buy-in. The use of Shewhart control charts was also covered, as a means to trend parameters of a system and to identify when problems are developing. The final section of Prof Gettinby's presentation looked at experimental design and Taguchi methods. If you want to know how to design efficient studies covering the appropriate variables, then this would be a good starting point.

Statistical Process Control and its application to pharmaceutical microbiological testing

The second presentation, by Tom Cochrane from NAPP Pharmaceutical Group, focused on SPC and the use of control charts to monitor performance. After explaining how to construct control charts and setting control limits, i.e. ± 3 sigma of mean, Tom described how to identify when problems were occurring in the process. There are well-defined rules of statistical control, such as a run of 7 data points increasing or decreasing, which indicate that the system is not performing correctly. In addition, all processes contain variation – it's a fact of life – the trick is being able to identify and understand the differences between Common Cause Variation, which is within operating limits for the system, and Special Cause Variation, resulting in an out of control process. Tom then detailed a number of applications relevant to microbiology that had benefited from SPC such as water and environmental monitoring, impact of changes to processes and also process validation. The benefits being:

- SPC increases the understanding of the system and its inherent variability
- SPC provides information on how to streamline the process efficiently and provide cost savings
- SPC allows identification of problems when they are starting rather than when the process is out of control
- SPC shows if remedial action has been effective
- SPC gives you nice graphs to show auditors and inspectors that your processes are within specification and controlled

However, while SPC is a useful tool in representing what is happening, it still requires a microbiologist to interpret the output from the method.



Setting environmental alert and action limits

Following lunch Eric Dewhurst, Head of Quality at IVAX, discussed his views and thoughts on setting environmental alert and action limits. A review of all the relevant definitions, regulatory rules and guidance documents and published views lead to the conclusions:

- It's all very confusing
- Environmental monitoring is semi-quantitative
- Monitoring must be tailored to specific processes
- All testing must meet the various average and individual guideline figures
- Use some sort of undefined analysis to detect trends in data and set action and alert limits
- Have a minimum count of 0 in each Class area and in Class 100 to have a running mean of < 1 CFU

One thing that did come out of the review was, that while there are people who understand the type of data generated during environmental monitoring and how to analyse it correctly, these are not necessarily the same people who tell the pharmaceutical microbiologist what action and alert levels they should have. Consequently there is a difference of opinion on the relevance of what is required to meet regulatory requirements.

Another point raised during the presentation was that while it is all well and good having defined numerical limits to work to, this does not remove the need for trained microbiologists to be able to objectively review the data and interpret what is being isolated. For example, if an area had a alert limit of 10 CFU, while a single plate of 12 *Staphylococcus epidermidis* exceeds the limit what about the 2 compliant examples of 3 consecutive counts of 7 CFU Gram negative at one location and a single mould isolated from 3 locations on the same day? These are both numerically below the alert limit so they must be OK!

Electronic data management - LIMS for microbiology

The final presentation by Dai Darkin, from AIS Ltd, provided an overview of Laboratory Information Management Systems (LIMS). Briefly, Dai described the potential of LIMS for handling the complete sampling process, from reception of material in the lab though to SPC of the data.

And to conclude ...

The day was completed by a panel discussion that reinforced the message raised in a number of the presentations. Although there are well defined methods for handling numerical data, to show that processes are in control, there is still an important need for suitably qualified and experienced microbiologists to review the implications of numbers and types of organisms being isolated.

Mike Wassall
GlaxoSmithKline Ware

Practical training on cleaning & disinfection a review

Following much consideration, deliberation, sleepless nights and a lot of hard work, thanks to Dr Rosamund Baird, Dr Anthony Smith, Rachel Blount and Poly Hajipieris, the first training package offered by PharMIG on the Practical aspects of cleaning and disinfection was established in January 2001.

This two-day course, at the pleasant surroundings of the University of Bath, was designed to provide an overview of the key microbiological issues involved in cleaning and disinfection and how that knowledge is applied in practice. It is relevant for scientists involved in microbiological contamination control, newly recruited auditors, those involved in the management of cleaning and disinfection for production supervisors and operators.



In any manufacturing process cleaning and disinfection plays a key role in the control of contamination. Any oversight or cleaning failure can lead to a delay in batch release and product failures. A detailed understanding of the principles behind cleaning and disinfection is of necessity if a successful sanitisation strategy is to be implemented. Due to the recent increased attention to the validation of cleaning and disinfection procedures by the regulatory authorities our practices should be supported by a rational approach based on accumulated microbiological data.



The agenda included disinfection theory, industrial guidelines and practices for both sterile and non-sterile areas, a practical laboratory demonstration, regulatory expectations, assessing case studies and an interactive audit workshop.

Dr Rosamund Baird, as the chairperson and Dr Anthony Smith hosted thirty delegates from a variety of pharmaceutical and hospital backgrounds.

We all arrived on a windy and stormy night, but the dinner and familiar faces made up for the bad weather. We found out about the campus and how to enjoy the university facilities. If I wasn't so tired I would have tried the Olympic size swimming pool or have a run around the university athletics and sports field, instead we tried out the local students bar!

On the first day Dr Smith introduced the course and dealt with a real world perspective on disinfection theory. He informed us of the method of application, concentration effects and rotation. We learnt about the physico-chemical properties of agents and their modes of action, together with issues of resistance and how they may impact on testing and validation. He paid particular emphasis on phenotypic resistance including consideration of the biofilm phenotype. We also considered the challenge of acquired resistance and the role of efflux systems in resistance to disinfectants.

Kevin Shade of Bio Products Laboratory summarised the surveys of industrial guidelines and practices, carried out by the PharMIG working group on disinfectant and cleaning practices in the UK in 1996 and by the PDA in the USA in 1997. From these surveys it was clear that very different procedures have been adopted and that there has not been a clear understanding of the requirements of the regulatory authorities. Other alternative procedures were also considered, eg CIP systems and complex and difficult-to-clean equipment. Biofilms on surface present a considerable challenge to the cleaning and disinfection procedures.

James Drinkwater of Bioquell Pharma discussed the requirements in biological decontamination and control; the types of controlled environments for which biological decontamination is a key requirement. We considered comparisons between biological decontamination methods, strengths and weaknesses, methods of choice, regulatory and safety, validation of cleaning, sanitisation and decontamination. James discussed the current trends in controlled environments in industry, laboratory and hospitals. We also considered the directives and guidelines.





Following an excellent well-earned lunch, the afternoon was spent with Karen Harrowing and Rebecca Anderson of the Aseptic Services Unit. We enjoyed a video presentation where the effects of the operator, the environment, the equipment, the disinfectant, the procedure and the validation of cleaning and disinfection system on quality of pharmaceutical products were considered. The video sequence provided a useful visual summary of the practice of cleaning and disinfection.

Having digested our lunch it was time to catch up on a series of practical demonstrations in the newly built Microbiology Laboratory. Ms Kim Morwood, Dr Anthony Smith, Dr Ros Baird and Mr Richard Pearce covered practical aspects of a variety of tests used in the determination of efficacy and validation of

disinfectants. A specified program of testing for chemical disinfectants and antiseptics, published by the CEN TC216 WG3, was discussed, the test procedures for BS EN 1650 and the bubble test were demonstrated.

There was a wide selection of prepared demonstration of environmental contamination from skin, hair, nail and clothing.

After a hard day of learning, it was time to relax. Following another wonderful meal some of us opted to recover, while others continued to soak up the alcohol. We even had time for a few rounds of snooker in between the pints!

On the second day, Dr Rosamund Baird discussed the role of environmental monitoring in contamination control. Areas such as sampling methods, equipment, standards and guidelines as well as MCA recommendations for Clean room areas were considered. This presentation provided a strategic approach to the control of contamination that included information on how to assess risk to product and to develop a monitoring programme.

So far the delegates had a very easy time but the case studies were a challenge. A particular case study was discussed in teams and then the team leader presented a summary report. It was a good opportunity and the right forum to iron out any pending and practical challenges that we would face back at the laboratory.

Mr Kevin Shade then updated us on the regulatory aspects of cleaning and disinfectant validation. This presentation provided very useful guidelines as the various regulatory authorities do not provide definitive guidance. It was clear that each company could provide documentary evidence of efficacy and to justify the procedures adopted and the methods used for testing. The CEN standards (BS EN 1276) was recommended as a useful basis for establishing a validation programme. The EC GMP guide and the FDA code of Federal Regulations give clear indications of importance of cleaning and disinfection.



The interactive audit workshop, presented at the end of the course, by Mrs. Sharon Johnson, was a practical and informative way to practice the skills acquired during this course. A variety of different areas that should be covered by an audit of cleaning and disinfection and monitoring programmes, training of cleaning personnel, cleaning effectiveness, test methods used in evaluating disinfectant agents.

The success of this course can be attributed to the hard work of all the dedicated individuals, including the presenters, organizers, delegates and the work carried out by the PharMIG working group on cleaning and disinfection. So for an update on the current scene in cleaning and disinfection why not try the next PharMIG course in Cleaning and Disinfection, planned for April 2002.

Arun Acharjya



Notice is hereby given of the first Annual General Meeting (AGM) of PharMIG limited.

The AGM will be held between 1630 and 1730 on Wednesday 7th November 2001 at the Peterborough Moat House Hotel, Cambridgeshire.

The AGM will have four sections

(i) Reports from present Chariman (David Begg), Treasurer (Bob Johnson), Secretary (Mary-Anne Weatherhead)

(ii) Election

- Anyone wishing to be nominated for any committee positions should either make their intention clear in this section of the AGM. If you are not attending the AGM please make your intention to stand for a position in writing to Poly Hajipieris (fax number 01992 478 675)
- All nominations must be proposed and seconded by an existing PharMIG member. This may be either at the AGM or prior to the meeting in writing to Poly Hajipieris (fax number 01992 478 675)

(iii) Open floor for members

(iv) Any Other Business

The committee positions are as follows

Chairman

- Chairs committee meetings
- Ensures group remains focussed and meets their objectives
- Ensures group remains focused to the needs of the members

Treasurer

- Organises company accounts
- Liaises with book-keeper
- Ensures that the accounts are managed effectively and efficiently
- Calculated pay back figures of all PharMIG events

Secretary

- Takes minutes at committee meetings
- Issues minutes within 2 weeks of the meetings
- Liases with administrator
- Update and issue standard operating procedures

Action Group Coordinator

- Coordinate various action groups
- Ensure action groups have everything they need
- Bring any issues raised by action groups to committee for discussion
- Help action groups to issue monographs with help from the committee
- Ensure action groups remain on track and focused

Communication coordinators (2 positions)

- Issue newsletter, this included organising articles and proof-reading
- Organise web site with web page administrator
- Ensure PharMIG meeting are relevant to members
- Ensure PharMIG meetings do not clash with other Pharmaceutical Microbiology meetings being held by other groups

External affairs coordinator

- Become involved with regulatory bodies to increase the profile of PharMIG limited
- Keep regulators informed of PharMIG meetings, so they are aware of the groups activities and share findings from action groups with them, with prior agreement from the committee
- Provide administrator with list of organistions / personnel that may be interested in PharMIG meetings.

Training session coordinators (2 positions)

- Plan and coordinate training sessions
- Plan and coordinate visits, either to Pharmaceutical sites or places of interest to members
- Raise any issues relating to training or visits at committee meetings



HACCP by Hazel Sarosi

Many companies are now adopting the Hazard Analysis and Critical Control Point (HACCP) system to generate a comprehensive review and summary of potential hazards identified for all manufacturing process.

HACCP is a tool used to systematically examine any process to ensure the prevention of known hazards occurring during a chosen process. Historically HACCP has been used within the food industry to ensure food safety but recently World Health Organization have published a draft of a working document 'Hazard Analysis and Critical Control Point (HACCP) for drugs and other pharmaceutical products', QAS/00.005. This draft document outlines the concept of HACCP as well as containing explanatory text and guidelines for its application with pharmaceutical products.

There are seven steps to the hazard analysis process, these are:

1. Analyze hazards

The first stage of implementation is to set up a small team. HACCP may include biological, chemical and physical hazards for any process. It is therefore wise to select a team with representatives from each of these disciplines. One of the most important parts of HACCP is identifying the hazards during this first step. It is imperative that a summary in the form of a flow diagram is prepared so that none of the potential hazards during a process are overlooked. Fig 1 is an example of the kind diagram that can be generated for the manufacture of a hard gelatin capsule.

A brainstorming session can often be very useful during which the team may review the starting materials, the activities that take place at each stage of the products manufacture from receiving starting materials to dispatch. Fig 2 is an example of the hazards that have been identified from the flow diagram in figure 1. At this point the hazard analysis only covers the microbiological aspects, but as has been previously stated, equally, this technique may be used for chemical and physical hazards.

Before proceeding to step 2 these identified hazards should be evaluated. A potential hazard must be evaluated on how critical it is to the process and or how likely it is to occur. The rationale for these evaluations should be documented before proceeding to the next stage.

2. Identify critical control points

Once critical hazards have been identified, specific control measures must be employed. One control measure may be to exclude something from the production area or as a result of HACCP a piece of equipment may need to be replaced. These are qualitative control measures. Other control measures may be quantitative e.g. controlling pH or humidity.

3. Establish critical limits for control points

Having identified control measures, critical limits within which the process needs to operate must be established. These values could be found by published work, regulatory guidance documents, or developed as part of process validation or development.

4. Establish procedures to monitor control points

Special consideration must be given to the frequency and practical aspects of monitoring control points. The point monitored must be representative of the process. For example it would be pointless sampling water directly from an outlet if when during manufacture a pipe was connected to this outlet.

The results from monitoring control points can be used in a number of ways. Firstly it may indicate to us when a critical limit has been exceeded. This enables us to make an informed decision in deciding what the impact may be on the product as well as being a precursor for any corrective action. Another useful approach may be to apply statistical process control and to trend the results so that any deviations can be seen in advance of a process becoming out of control.

5. Establish corrective actions

Within any good quality system there must be a mechanism for the quick and effective implementation of corrective actions. These will usually be written procedures outlining exactly what action needs to be taken when the critical limits have been exceeded

6. Establish a record keeping system

In the true spirit of GMP, if it is not recorded it did not happen!

7. Establish procedures to verify that the system is working

Finally, the HACCP plan should be regularly reviewed as part of the verification process. HACCP documentation is created to be as dynamic as our industry environment is.





Fig 1. Summary of Typical Manufacturing Process for Hard Gelatin Capsules¹

Step	Process	Operating Procedures	Potential Hazards
1	Premixing	Charge components into a diffusion blender (active plus excipients). Blend components for 10 minutes.	- Contamination from equipment and excipients
2	Screening	Pass the product through screening mill (rotating impeller) fitted with 500mm pore-size mesh.	- Contamination from equipment
3	Mixing	Mix in a low shear mixer / granulator for 10 mins at low speed	- Contamination from equipment
4	Wet - Granulation	1. Wet with purified water in the same mixer / granulator over a 20 minute period while mixing at low speed. 2. Granulate the wet product for 5 minutes at medium speed, then 3 minutes at low speed.	- Contamination from equipment - Contamination from purified water
5	Drying	Dry the wet granules at 55oC in a directly heated, fluidised bed dryer.	- Contamination from hot air
6	Sizing	Reduce the particle size by sizing in a screening mill (rotating impeller) fitted with 500mm pore-size mesh.	- Proliferation hazard due to warmth and moisture
7	Admixing	Charge into a diffusion blender, add further excipients to blender (e.g. mag stear) through a mesh of pore-size 315-355mm. Admix components for 5 minutes. Sample blend for homogeneity and physical characterisation of the blend.	- Contamination from equipment - Contamination from equipment - Contamination from personnel during sampling
8	Encapsulation	Fill capsule blend into capsule shells.	- Contamination from equipment
9	General	Manufacturing process	- Contamination from the environment

Fig 2. Potential Microbiological Hazards of the Manufacturing Process for Solid Oral Dosage Forms



cartoonist - profile

There have been many David Jones in the world but I can assure you, this one is the definitive article.

I have known David Jones (aka Jonesy) for more than ten years. Some of this pen portrait is from memory and some is from interview over a few pints of Black Sheep in the Tap & Spile in North Shields.

Jonesy was born in 1968 into a life of crime, literally. He was delivered at home in a Borstal in Newton Aycliffe. Showbiz people usually take a few years of their career to get to rehab. Jonesy got there on the day he was born.

His parents weren't victims of society, however they worked there. After this inauspicious start who would have thought his temperament would lie with the Arts.

Shortly after rehab, Jonesy moved from the North East to Hereford, where he was to spend the rest of his childhood.

The first inkling of his artistic talent appeared when Jonesy won a national cartooning competition. He was sixteen and his reward was to meet the late, great Willy Rushton and spend a week honing his skills with a lady. Encouraged by his success Jonesy published pamphlets of his and his friends work.

After school, Jonesy read Philosophy at Manchester University. An outstanding scholar Jonesy always got a first for his essays and dissertations. This is where I met him.



He was attempting to flog his self published comic book in the bar.

Jonesy sustained himself at college with a diet of Special Brew and roll-ups (the odd curry provided basic nutrients). It was said you could never offer Jonesy a cigarette because he always had one in hand.



We shared a house together in Chorton-cum-Hardy opposite the animation studio, which produced Danger Mouse. This must have inspired Jonesy as he demonstrated his heroism during a fire next door.

He was part of a human chain in a daring roof top rescue. It made the front page of the Manchester Evening News no less.

At this time Jonesy had already begun to get work for Viz. His first Character being the incomprehensible Roger Irrelevant.

After University and various publications Jonesy move to the Isle of Anglesey- famous as a haven for retired alcoholic writers. He became a regular contributor to Viz comic.

While there Jonesy rescued a Dobermann from a cruel farmer, the poor mutt was tethered starving and lame. He named the dog Woodbine ('cos he took it for a drag in the morning). Sadly it died a couple of years later (cancer I think).

Eventually, Jonesy was invited to Newcastle-upon-Tyne by the editor of Viz to take up a post on the Editorial Cabinet.

Jonesy now lives in Heaton where he keeps rats. PharMIG recruited Jonesy on a voluntary basis and he has kindly submitted a number of comic strips to the PharMIG newsletter.

Martin Sarosi PharMIG Webmaster

