Upjohn

# Control News

INTERNATIONAL TECHNICAL EDITION SECOND QUARTER 1989

*Graham Laker (U.K.) working in the La Calhene sterility testing unit.*

# Globalizing Registration

*Jan Spitael*

To place a product on the market, a major task for The Upjohn Company is to obtain approval from the regulatory authorities.

The process of registration is complex and differs from country to country. Whereas most subsidiaries of Upjohn are only involved in the final registration of the finished product, a number of operations throughout the world are also involved in filing applications to obtain authorization to perform clinical trials in a specific country. The Control Division plays a key role in all of these activities.

I would like to highlight some of the features that are related to a worldwide registration approach, as opposed to an approach on a country-by-country basis. The Upjohn Company has recognized that in order to operate on a worldwide basis it needs to "globalize" the operations. The Control Division is probably at the forefront of this globalization effort.

**Is It a Challenge?**

The answer to this question is a definite "yes". Why? Just saying you will operate on a worldwide basis does not mean everybody knows what should be done to achieve it. An extensive education process is needed for the people involved, to come to an understanding of the differences and similarities in the world we are living in today.

The Food and Drug Administration (FDA) has specific requirements on what should be included in a New Drug Application (NDA) for a Human Health Product. Animal Health Products are subject to another set of requirements for the New Animal Drug Application (NADA).

In Europe however, there is

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# UK Renovates Biology Lab

*by Ian Williams*

This year saw the completion of a three year consolidation and refurbishment program for the Biology Section of the Control Laboratory Operations Group in the UK. In 1986 the section consisted of a separate environmental control and microbiology unit which was responsible for assays, animal work and sterility testing. Both these units had a separate infrastructure and were physically separated from each other, which was not an effective or efficient use of manpower. In 1986 a decision was taken to phase out the manufacture of sterile formulations and to increase the manufacture and range of non-sterile formulations produced at the Crawley site. However, this still left a sterile manufacturing presence in the Research Division which had to be supported by Control with all the attendant activities involved. This provided an ideal opportunity to begin a restructuring program which would lead to a more effective use of manpower and also would provide the laboratory facilities which were required for the foreseen future operations.

The personnel plan was started in late 1986 with the emphasis of cross-training under one management structure. This has been a success in the creation of a workforce with an increased skills component which allows the reallocation of staff to meet changes in the workload. As an added bonus, this resulted in manpower savings which have been utilised elsewhere

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# Registration *(continued from page 1)*

*Meeting the challenge for a global registration program to support all marketed products.*

little or no difference in the requirements for Human Health Products or Animal Health Products. In developing new products, it is therefore essential to incorporate the "worldwide" requirements as early as possible into our Control activities and plans. It should help the Development Group in focusing on the essentials, and concentrate, upfront, on the typical challenging assays such as tests on impurities and degradation products.

In terms of specifications, it is remarkable that 90 to 110% limits for the potency of the active substance in a dosage form are still a standard in the U.S., whereas 95 to 105% limits become the standard in Europe.

Japan has brought some other "typical" specifications. A limit test for Arsenic is standard for bulk drugs, as is a limit test for "Heavy Metals".

**Regulatory Requirements—A Changing Environment**

As the scientific knowledge of pharmaceuticals increases, the same can be said for the regulatory agencies. With time, the requirements are due to become more stringent. Increasing consumer awareness can create additional concerns for the regulatory people, sometimes going beyond any scientific reason for new requirements. Because of this changing environment, a good monitoring program must be in place to find out how new regulations might affect our business.

A major change is currently occurring in Europe. The year 1992 has been called the year of "unification" of Europe. With the elimination of trade barriers, the legislators have started an extensive program in Europe which is commonly referred to as the Re-Registration Program.

Up to now, standards have been quite different from one country to another, as each government addressed the matter at a local level. With legislation at the European level, common standards have been developed and the different countries have requested the pharmaceutical companies to bring their product applications up to those common standards. The way this is being accomplished varies from country to country, but one thing is sure, we have to do it too!

***Specifications Development Group: Seated are Christine Walker, Ed Knoechel, Bonnie Solter, Jan Spitael. Standing are Marcia Greko, Carol Clark-Evans, Brian Hoff, Tom Oslind, Dorothy Frank, and Ellen Harrington. Not pictured is Barb Ray.***

As in Europe, where some of the older Upjohn products are marketed, this has created the need to review older applications and to upgrade these files to today's standards. This is not an easy task, as we are at the same time developing new products. The allocation of resources plays a very important role. With time we can expect similar requests to update older files for the United States FDA. As a result, we anticipate the need for a global program to support all marketed products on a worldwide basis.

**Post Scriptum**

With the increasing availability of modern technology, the world is becoming smaller and smaller. With the Concorde, you can be in Paris or New York in a couple of hours. You pick up the telephone and call your colleague in Tsukuba, Crawley, Indonesia, Colombia, or downtown Kalamazoo. The Upjohn Company is committed to operate on a worldwide basis. The Control organization has been, and will be, changing in support of the Corporation's direction. To be successful we, the people in Control, have to make it work. ◆

# New Control Manager

*We would like to introduce our new Control Manager at Upjohn Farmoquimica, S.A., Madrid, **Spain**. . .*

***Amparo Portero, Spain***

**Amparo Portero** studied at the university in Madrid, obtaining a degree in Microbiology in 1979, and was hired at the Upjohn subsidiary, in Madrid, Spain, the same year. As an analyst, Amparo worked in the Microbiological and Environmental Laboratory for three years.

She was promoted to Micro Lab and Environmental Control Supervisor, and in 1987 she joined the QA Unit as Supervisor. In first quarter 1989, Amparo was promoted to Control Manager at Upjohn Farmoquimica, S.A., in Madrid.

Amparo resides in Madrid with her husband and two young children. She enjoys outside sports and reading, but mostly she enjoys her involvement in family activities. ◆

# Lab Renovation *(continued from page 1)*

***Ian Williams, UK***

***An opportunity taken for more effective use of manpower and to provide lab facilities to meet requirements for future operations.***

within the Control Division.

The existing laboratory was of a design fifteen years old and was not instrument or computer compatible; factors which would lead to problems in the future. Laboratory support for antibiotic assays, sterility testing and biological evaluations were still required, but the methodology would change to rely more on the use of computerised instrumentation. In addition, the frequency of performing some evaluations would fall, but the relevant skills and facilities to perform the evaluations would still be required. This need was reflected in the choice of laboratory design and equipment which was in the project plans that were submitted for approval.

The project involved the renovation of 160 $m^2$ of laboratory area in three phases, as well as connecting the microbiology area to the existing environmental control laboratory. The laboratory/equipment had the following features incorporated:

1. The laboratory was equipped with service utilities making it compatible with instruments, as well as connections to the Control Computer System, to facilitate the use of HPLC for antibiotic assays. In addition, sufficient extraction and fume cupboards were installed to increase the flexibility of the type of analyses that could be performed.

2. A "stand alone" sterility testing system was purchased from La Calhene, a French manufacturer, which negated the need for gowning procedures or complex air handling systems to be maintained in the sterility testing area. This also allows greater utilisation of the area by allowing the locating of incubators and storage cupboards within the testing room. The unit can best be described as a plastic bubble supplied with HEPA-filtered air and isolated from the room environment by small air locks. The unit is sterilised by a gassing technique and the operator performs the sterility test by working in a half-suit which is built into a plastic wall of the unit. This allows the performance of sterility testing at a significantly reduced maintenance cost per test. In addition, the unit can be converted to a negative pressure testing environment. This will be of importance where the emphasis is on operator protection when dealing with toxic formulations.

In addition to the above major items, two additional pieces of equipment were installed at the end of the project, both of which reduce the amount of operator intervention in producing data:

1. An image analysis system which is to be used to read antibiotic assay plates as a replacement for the current manual measuring system. In addition to this function, it will also be used to enumerate microcount and preservative efficacy samples.

2. A temperature monitoring system for essential incubators which records data automatically on a continuous basis.

Work started on the project in January, 1988, and all phases of refurbishment were completed by the autumn. The major problem was keeping the unit operational during this time and the laboratory autoclave in operation. This was accomplished by moving staff temporarily to other parts of Control and relying heavily on staff patience and forbearance. It was through the efforts of all concerned in this project that there were no major problems and the work was accomplished ahead of schedule. Well, I guess the biggest question to be answered is whether the program is a success and was the objective achieved. The answer to this is "yes." The amalgamation of the units is complete, there has been a reduction in manpower, the pool of expertise has been increased (and is still increasing in the area of chemical analysis), and systems and facilities have been provided which facilitate sufficient flexibility to enable the Biology Section to operate effectively to meet the forecasted workload. ◆

***The new UK Biology Laboratory.***

***Ann Lewis using the new Image Analysis System.***

Control News
INTERNATIONAL TECHNICAL EDITION

**Published Quarterly by:**
Quality Assurance—
Offshore Operations

**Editors:** K. M. Harriger
D. C. Mitchell

# IPRD: The Crawley Perspective

*Jane Smith*

*Robert A. Pizzie*

New products are of fundamental importance to the continued viability of The Upjohn Company and it's subsidiaries. The International Product Registration Document (IPRD), which is prepared by the Specifications Development Group, in Kalamazoo, and contains the chemistry/pharmacy information for new products, has an essential role to play in the system for introduction of new products to subsidiaries such as Upjohn UK, Crawley. The following paragraphs describe the way the IPRD has been used in the past at Crawley, some problems encountered with this approach, and a number of recent improvements, both to the document and to it's use, which point the way for the future.

Traditionally, the format and content of the IPRD has reflected the requirements of the FDA, rather than those of the European Community (EC). For example, the IPRD would typically quote the United States Pharmacopoeial, rather than the European or British Pharmacopoeial monographs as the quality standards for excipients or active components. Additionally, no Expert Report (a critical review of the chemistry/pharmacy data prepared by a recognised "expert", which is required to be supplied with every licence application submitted in the EC) has been provided with the IPRD. Historically, the IPRD has been sent from the Specification Development Group of the Control Division, in Kalamazoo, to the Health and Regulatory Affairs (HRA) Division at Crawley. HRA has then used the document as the basis for the preparation of the chemistry/pharmacy file for Product Licence Applications to the Department of Health, UK, The Ministry Of Agriculture Food and Fisheries, UK and the National Drugs Advisory Board, Ireland. The IPRD is a generic document which requires "fine tuning" to reflect the facilities, equipment and processes of the local subsidiary. This "fine tuning" is performed primarily by the subsidiary Control and Technical Services Engineering (TSE) Divisions, yet these groups were not required to contribute directly to the preparation of the original registration application. Typically, the Control and TSE Divisions would only become involved once the file had been submitted to the Regulatory Authority and questions had been received from the chemistry/pharmacy reviewer. The limitations of this approach have become increasingly apparent as pharmaceutical product regulations have become more stringent, and registration application review more sophisticated.

Recently some improvements to the content of the IPRD, as well as the systems used to prepare chemistry/pharmacy sections of applications, have been implemented.

Since mid 1988, the format of the IPRD has been modified to reflect that required by the EC. This has significantly reduced the amount of work required to prepare chemistry/pharmacy sections of product licence applications. More recently the IPRD for ROGAINE® Gel was supplied as a WordPerfect file on a diskette, thereby eliminating the need to retype the document. With the recent implementation of systems which enable Control in the UK, to access the Control Kalamazoo Computer Network, the possibility of electronic transfer of information offers some exciting possible extensions of this initiative. Generic Expert Reports are now being prepared by the Specifications Development Group in Kalamazoo and included with the IPRD. At present, these tend to be summaries of the IPRD rather than critical evaluations of the information presented and significant effort is still required locally to ensure compliance with regulations.

The procedure for preparing regulatory submissions from IPRD information has been modified to include significant input from the Control and TSE Divisions. The IPRD is still sent to the HRA Division at Crawley which prepares the chemistry/pharmacy file in accordance with the EC Guidelines for Product Licence Applications "Notice to Applicants" (Doc:III/118/87). Any questions arising during this process are passed to TSE or Control and replies are incorporated into the file. The draft file is then passed to Control for review and preparation of the EC Expert Report utilising the generic Expert Report, provided with the IPRD, as a starting point. The completed and approved expert report, along with the reviewed file, are then returned to HRA for submission to the UK and/or Irish Authorities. These files and expert reports are also supplied to the Control Division of other European subsidiaries for which the UK is the source country for the product in question. The improvements detailed above have already resulted in a significant increase in the

*(continued on page 8)*

## What is an IPRD?

An IPRD (International Product Registration Data) is a collection of information which can be used to accomplish human pharmaceutical registration approvals in countries outside the US. The document contains general product information, chemical and pharmaceutical data, toxicological and pharmacological data, clinical data, and product-specific particulars. It may be submitted "as is", but often times Health Regulatory Affairs (HRA) personnel in individual countries prepare registration applications from the information contained in the IPRD. Recently, Kalamazoo personnel prepared the IPRD in the European Economic Community (EEC) suggested format so that subsidiary personnel can include portions of the IPRD "as is" in their registration applications. Each subsidiary has its own unique set of regulatory requirements. As a result, what happens to the IPRD after it gets to the subsidiary varies. In the accompanying article, Rob Pizzie and Jane Smith summarize what happens to the IPRD in our UK subsidiary.

# 1992: Trade Barriers Fall in the EEC

***Colin R. Broom,*** *Brussels*

***Product Registration Process — "What changes might occur in conjunction with free movement of pharmaceutical goods within a single European market?"***

**Background**

The European Economic Community was established by the Treaty of Rome in 1958 and signed between the original six member countries (Belgium, France, West Germany, Italy, Luxemburg and The Netherlands). These original member countries have been joined over the intervening years by Denmark, Greece, Ireland, Portugal, Spain and the United Kingdom, bringing total membership now to twelve.

One of the major objectives of the Community is to create a single market within the EEC and, thus, the free and unrestricted movement of goods between member states by 1992. Consistent with this objective, the Commission of the European Community has to decide by November, 1989, on a system for the evaluation and registration of pharmaceutical products in the Community in order for the free movement of pharmaceutical goods to take place.

**The Current Situation**

At the moment, three systems exist by which a pharmaceutical company may obtain approval for the marketing of its products in member states.

1. Individual approval in all 12 member states may be obtained by individual license application submissions in each of the 12 EEC countries.

2. The CPMP Multistate Application Procedure (see Table I), which is based on Mutual Recognition, whereby, after registration approval in one member state, the application can be extended to at least two other member states on the basis of the same documentation. The member states must consider the original authorization, involving also the opinion of the Committee for Proprietary Medicinal Products (CPMP) in the case of serious objections against license approval.

3. The "Bio/High Tech" Concertation Procedure (see Table II) by which the CPMP must be directly involved for biotechnological products. The system is optional for high-tech products. It is founded on an exchange of views before any national decision is taken, and should consequently be likely to facilitate a uniform decision and lead to a centralized European opinion.

Experience with the CPMP multistate procedure now spans several years. The evidence suggests that the system has not been a resounding success. The attitude of national licensing authorities seems to have contributed to the relatively poor experience of the system to date because of an apparent inability to agree on licensing decisions. This either reflects a lack of trust between licensing authorities or fundamental differences in approaches to therapeutics in each member state.

The move towards a supranational regulatory opinion from the CPMP in the "Bio/High-Tech" concertation procedure should be

*(continued on page 7)*

**Table I**

CPMP MULTISTATE APPLICATION PROCEDURE (83/570/EEC)

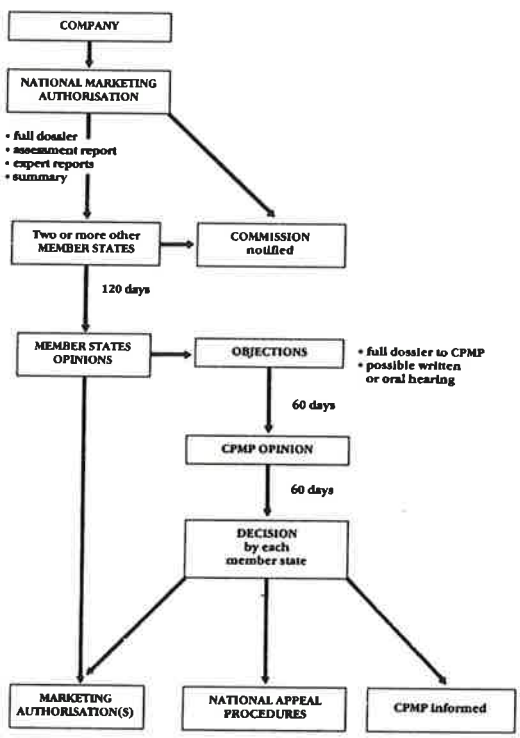
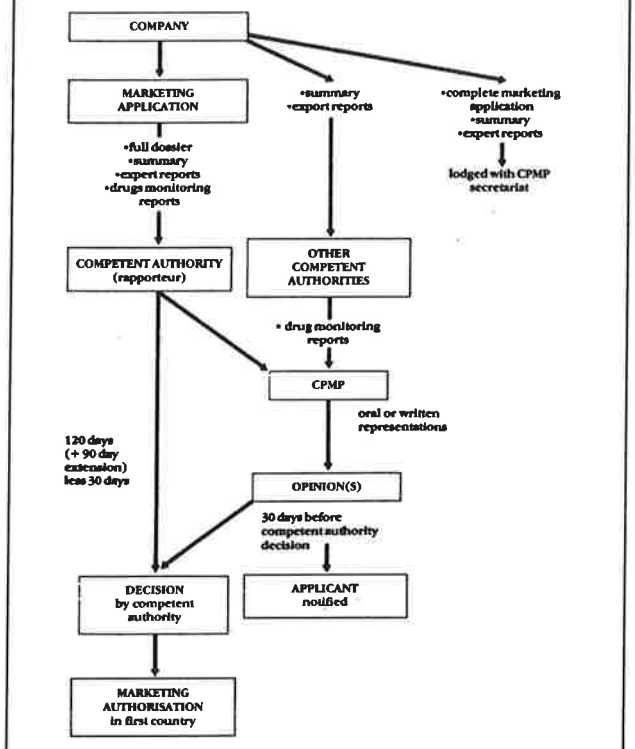



**Table II**

'HIGH-TECH' CONCERTATION PROCEDURE (87/22/EEC)



# *Safety:* Dangers of Peroxides

***Donald C. Gruber***
***QA International***

***Recognizing chemical structures — critical to safe handling practices in the laboratory.***

Recently a situation occurred in Kalamazoo that could have resulted in serious injury to laboratory personnel. While looking for a reagent, an analyst discovered a bottle labeled THF waste containing a crystalline precipitate thought to be peroxides. After consultation with the Health and Safety people, the peroxides were destroyed by an outside contractor using the proper techniques. However, this case reminded us that all laboratory personnel should be aware of the dangers of peroxide formulation in laboratory chemicals and reagents.

Peroxide formation has been the cause of many laboratory accidents. Recognizing chemical structures that are potential peroxide formers is critical to the development of safe handling practices for these types of compounds. Normally, when a compound contains one of the structures shown in Table I, it is a potential peroxide-former and is a potential hazard. Table II is a partial list of common peroxide-forming chemicals.

Control has formulated guidelines to be used in the handling of peroxide forming chemicals. Since peroxide formation can occur readily in some chemicals, with the process accelerated by contact with air and exposure to light, the following practices should be observed.

1. Use material that contains an oxidation inhibitor.
2. Institute a strict program to date all peroxide-forming materials detailing the date received and date opened.
3. Store the material in its air-tight container, away from light.
4. If it is a material that forms peroxides with ease, dispose of within one month from the date it is opened. All other peroxide formers should be disposed of within three months of opening.
5. Purchase the smallest container available.
6. Do not open or handle if you find material that is old or has crystals; treat as an explosive.
7. Put a nitrogen blanket into the container to limit the air contact with the peroxide former before closing a container.
8. Properly dispose of a container within one year of receipt, even if a container has not been opened. ◆

**Table I**

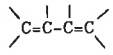
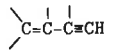
| | ORGANICS | INORGANICS |
|---|---|---|
| 1. |  Ethers, acetals | 1. Alkali metals, particularly potassium |
| 2. |  Olefins with allylic hydrogen, chloro- and fluoroolefins, terpenes, tetrahydronaphthalene | 2. Alkali metal alkoxides and amides |
| 3. |  and  Dienes, vinyl acetylenes | 3. Organometallics |
| 4. |  Aldehydes | |
| 5. |  Ureas, amides, lactams | |
| 6. |  Vinyl monomers including vinyl halides, acrylates, methacrylates, vinyl esters | |

**Table II**

**PEROXIDE FORMING CHEMICALS**
**(Partial Listing--those which form peroxides with ease)**

| | | |
|---|---|---|
| Acetyl | Decalin | Di-n-propoxymethane |
| Allyl Ether | p-Dibenzyloxybenzene | 1,2-Epoxy-3-isopropoxypropane |
| Allyl Phenyl Ether | 1,2-Dibenzyloxyethane | Isophorone |
| iso-Amyl Benzyl Ether | Diethoxymethane | beta-Isopropoxypropionitrile |
| Benzyl n-Butyl Ether | Diethyl Ether | Isopropyl Ether |
| Benzyl Ether | Diethyl Fumarate | n-Propyl Isopropyl Ether |
| Benzyl Ethyl Ether | Diisopropyl Ether | Tetrahydrofuran |
| Benzyl 1-Naphthyl Ether | 1,1-Dimethoxyethane | Tetralin |
| Chloroacetaldehyde Diethylacetal | Dimethoxymethane | 1,3,3-Trimethoxypropene |
| 2-Chlorobutadiene | 2,2-Dimethoxypropane | Vinylidene Chloride |
| Cyclohexene | Dioxane | Isoamyl Benzyl Ether |
| Cyclooctene | 1,3-Dioxepane | |

# EEC *(continued from page 5)*

attractive to industry. Experience with this procedure is very limited as it only came into force in July 1987. The scheme is likely to be utilized voluntarily by the industry for other novel products (i.e., high technology products) since the concertation procedure should enable the issue of a harmonized marketing authorization in a short time frame throughout Europe.

**Future**

By October 1989 the CPMP, reporting to the Director General for the Internal Market must propose to the Commission, who will in turn submit to the Council a proposal containing "appropriate measures leading towards the abolition of any remaining barriers to the free movement of proprietary medicinal products".

In essence, there are still two possible basic methods for registration approval:

1. "Mutual recognition," perhaps through some sort of Multistate Application Procedure, remains one of the options. This fits ideally the concept of "free movement" and "single market", but the system is not generally accepted.

The fact that member states have shown reluctance to take into due consideration, save in exceptional cases, each others decisions leads to the conclusion that they may not be totally committed to a mutual recognition system.

2. A "centralized system" would set up a central review and approval organization for all EEC countries (an FDA-type organization for Europe).

This system, in general, would be favored by politicians but is not favored by the regulatory authorities or industry.

There is a good deal of disagreement both between and within the interested groups (the pharmaceutical industry, the authorities, the politicians and the consumers). The various parties are considering a variety of options and modifications to the two basic systems. The Commission is continuing to look seriously at all possibilities before making a final recommendation.

Although the pressures to achieve a unified system for medicines regulation quickly and to complete the internal market by 1992 are very great, the timetable to achieve the progression towards this objective may not be met. In practical terms, all the complex changes in provisions which will be necessary and, more importantly, the acceptance and recognition of changes in responsibility between national competent authorities and any supranational body may take longer. ◆

# *Management Corner:* Perspective

The ability to change a point of view—to get a fresh look at things—is the mark of good managers and supervisors. This is particularly true in judging those who work under them. People change. some grow and develop, others slip into complacency and apathy. A good leader keeps abreast of these changes, whether for good or bad.

Long-time employees, for example, who have handled their jobs for so long it's hard to picture them doing anything else, often get taken for granted. They don't complain, so you tend not to think about them. The truth may be, however, that they have outgrown the job and are ready for something bigger.

Many people, blocked in their companies, have quietly accepted jobs in other companies and surprised their former associates by moving rapidly ahead to greater achievement. Why? Because the new employers took a fresh look at their capabilities and gave them a chance to use them.

To keep good people from growing frustrated, it's necessary to notice their developing talents, and find a way to put them to use. "The only person who behaves sensibly," said George Bernard Show, "is my tailor. He takes new measurements every time he sees me. All the rest go on with their old measurements."

True, some people reach the limits of their ability. Greater demands would only get them in over their heads. But most people keep learning and growing, far more than their bosses sometimes recognize. Keeping people in jobs they've outgrown isn't good for them or the company.

If people are doing well in their present assignments, for example, what else can they do? Is there some way to test their capacity with other tasks?

If they've mastered one responsibility, can you enlarge it by giving them something new to worry about?

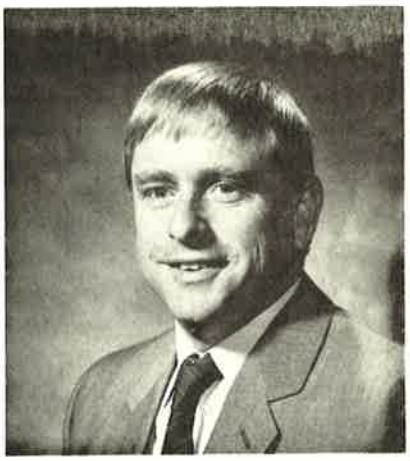
If some people show special abilities, can you give them more problems in that area?

It also helps to share your own responsibilities—to the extent that associates show they can carry them. It keeps them reaching and growing.

Whatever you do, be careful not to underrate people. A new look may surprise you. Visualize the man or woman in a more challenging situation. What counts is not what they were capable of yesterday, but what they can do for the business today and tomorrow. ◆

(Bits & Pieces, December, 1987)

# *Visitors . . .*



*Jane Smith*
*Peter Haegens*

We were pleased to have the following visitors with us in Kalamazoo during this past quarter.

**Jane Smith**, Control Record Systems Manager, resides in West Sussex, with her husband Charles, and is employed by Upjohn Limited, in Crawley, Sussex, England. She received a bachelor of science degree from Loughborough University of Technology in 1979 and was granted a master of science degree (analytical chemistry) from Chelsea College, University of London in 1984. Prior to joining Upjohn, Jane was employed by Whatman, Ltd. for two years and Goldwell, Ltd. for one year. Jane enjoys travel and walking in her leisure time.

**Peter Haegens**, Microbiologist/Analyst, in Australia, was in Kalamazoo for a Control training program. Peter was born in Holland and raised in NSW, Australia. He received a degree in microbiology from Newcastle University, NSW. Peter was employed by B.H.P. Steel International for eighteen years. For two years he worked for Watertel Engineering, a firm dealing in water treatment chemistry and equipment design, prior to joining the Upjohn subsidiary in April of 1988. A few interests of Peter's include photography, fishing, sailing and carpentry. Peter's wife and three children are joining him in travels which included this trip to Kalamazoo.

**Other visitors to Kalamazoo Control** were **J. Albors**, Control Director, UMC, Puerto Rico; **C.R. Broom**, Control Manager, European Operations, Brussels; **M. Castro**, QA Manager, UMC, Puerto Rico; **B.J. Dale**, Control Manager, Canada; **R.J. DeVries**, Control Manager, Belgium; **S. Hossain**, Microbiologist, Canada; **J. Morrison**, Plant Manager, TUCO Canada; **J.M. Nivet**, Control Manager, France; **R.A. Packer**, QA Manager, England; **M. Pellegrini**, Control Manager, Italy; **A.M. Pellim**, Control Manager–Rhodia, Brazil; **A. Portero**, Control Manager, Spain; **K.F. Roller**, Control Manager, TUCO Canada; **S. Tischler**, QA Manager, Canada. ◆

# IPRD: Crawley *(continued from page 4)*

quality of regulatory submissions for new products.

Whilst the situation is much improved for new products, significant challenges are being faced for existing products. The UK, along with the other countries in the EC, is in the process of supplying review files to the National Regulatory Authorities for currently marketed products. This activity is being pursued in preparation for 1992 when trade barriers in the EC are scheduled to be eliminated. The intent of the EC is that all pharmaceutical products sold within it's bounds will conform to common quality standards, consequently the files submitted are being reviewed by the authorities for compliance with current EC guidelines. This represents a significant problem, as the older IPRD's do not include all the information required. For example, little or no information on development pharmaceutics, assay validation, process validation and impurity/degradation products are included in most of these documents. Questions on several products already submitted under the review programme have been received from the authorities and more are expected between now and 1992. Where the data is not available to provide responses to these questions, laboratory work is being conducted both in the UK and Kalamazoo to supplement the files. For files not yet submitted a proactive stance is being taken and attempts are being made to update IPRD information prior to submission of the review file.

The group within Control UK with responsibility for registration support is Control Records Systems (CRS). As well as review of chemistry/pharmacy files and preparation of the EC Expert Report, this group provides stability data and analysis to support shelf-lives for registration files or to extend an approved expiration dating, copies of Control specifications and procedures for inclusion in registration files and responses to specific regulatory questions forwarded by export customers.

Significant improvements have been made both to the content of the IPRD and the systems whereby the information is transformed into regulatory submissions in the UK. These improvements have been achieved through the commitment and professionalism demonstrated by all parties involved, as well as increased provision of resources by management. This investment of resources must continue to allow further improvements to be realised. ◆

***"Reading is to the mind what exercise is to the body."***