Country *Profile*

A look at the
Pharmaceutical Industry in

SINGAPORE

Produced in collaboration
with ISPE Singapore

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This new feature in *Pharmaceutical Engineering* is designed so that you can tear it out, three hole drill (if desired), and keep it with other Country Profiles as they are published.

Look for the Country Profile on Belgium in the September/October issue of *Pharmaceutical Engineering*.

Dear ISPE Members and Readers,

It is with great pleasure that I present the Singapore Country Profile in this issue of Pharmaceutical Engineering. I am Italian, and as probably many of you know, Italians are very proud of the natural and artistic beauty of our country. However, even with such high standards, I have fallen in love with Singapore's tropical climate, green vegetation, high technology, culture, and people since my plane landed at Changi airport more than two years ago. Although the most endearing attribute to this city-state is the people who are always keen to smile, try to help you even for the most trivial things, and have a great capacity for learning. It is with this personal joy and conviction of the merits of Singapore that I introduce you to this short, but hopefully informative and interesting microcosm of the world of pharmaceuticals in 2003 and beyond in Singapore.

Singapore is a young, vibrant country formed by a friendly split with Malaysia in 1965. Its primary assets are its location, harbor, stable climate, and people who at around 4.5 million (more than Ireland) have transformed it over this period into the worlds busiest harbor, largest refinery area, and a top ten global economy. This is all based primarily on manufacturing and the process industries; and the bio-sciences have been targeted as one of the high technology intellectual property sectors for future growth.

While the first multi-national pharmaceutical company manufacturing semi-synthetic antibiotics came here in the early 1970s, our manufacturing industry has significantly grown in the last 5-7 years. Singapore, with a pharmaceutical plant investment of approximately $3 billion, is probably the most dynamic and innovative biomedical hub in Asia outside Japan. Activities range from a growing basic research and development base, API, drug products, and parenteral biotech proteins manufacture to a large regional center for clinical trials.

Its Economic Development Board is actively selling around the world Singapore as an integrated, strategic global bio-science location. It is a politically stable, relatively low cost environment with an ethically strong business and government culture and hard working people. It has an equal or greater growing population of skilled staff (both for production and service industry) as any other equivalent pharmaceutical center, to meet the expected growth in new plants, and sufficient newly created land to support a trebling of the current plants at least. The Government Financial packages are more than attractive.

I hope you will find this Singapore Country Profile interesting enough to put Singapore in your sights when the subject of a new pharmaceutical development location is discussed. Who knows, a cold tiger beer, a bowl of tasty laksa, and the ancient culture of the Asian continent await you once your facility is completed and operational, together with a sound financial return on your investment!

Yours Truly,
Dr Ing Roberto Gardellin
Chairman, ISPE Singapore Affiliate

Singapore - The Premier Biomedical Hub of Asia

by the ISPE Singapore Affiliate

Singapore has enjoyed phenomenal growth over the last four decades despite its small size and population - just 4.5 million people - and lack of natural resources. Its per capita Gross Domestic Product (GDP) has been growing at an average annual rate of 10.5 %, swelling from $512 in 1965 to nearly $21,000 in 2002, and now trails behind only Japan and Hong Kong for the highest per capita income in Asia.

Despite its historical importance during its days as a British crown colony as a strategically located trading port linking the West with the East, Singapore's miraculous economic growth has been achieved by focusing on manufacturing and productivity. It built shipyards, attracted global oil refineries to build on reclaimed land, and later followed the technology wave onto manufacturing and now designs of disk drives and semiconductors.

Today, manufacturing and services are the twin economic engines of growth, with the chemicals, electronics, and the engineering clusters as the key pillars of Singapore's economy.

To diversify and strengthen Singapore's economic resilience, the government has been aggressively developing the Biomedical Sciences cluster as another key pillar of the country's economy. Since June 2000, this initiative is jointly driven by the Biomedical Sciences Group (BMSG) of the Singapore Economic Development Board (EDB) and the Biomedical Research Council (BMRC) of the Agency for Science, Technology, and Research (A*STAR). EDB is the Government body responsible for industrial development while A*STAR funds, coordinates, and directs public research, as well as promotes public awareness of science and technology in Singapore.

In addition, an International Advisory Council comprising pre-eminent scientists from the US, Europe, and Australia advises the government on various biomedical initiatives covering R&D, industry development, education, and healthcare. The Council is Chaired by Sir Richard Sykes of Imperial College in London and Co-Chaired by Dr Sydney Brenner of the Salk Institute for Biological Studies in California.

A Timely Boost To the Economy

As the country emerges from one of the worst recessions since its independence, the solid performance of the pharmaceutical industry has provided a timely boost to the economy. Measured on a year-on-year basis, the sector has shown strong and consistent growth in total manufacturing output, jobs creation, and value-added for the past five years.

Merlion overlooking Singapore River.

Singapore Fact Sheet (2002):

Physical Facts
Population: 4.5 million
Land Area: 682.3 sq km
Average Daily Temperature: 26.8 - 31°C
Annual Rainfall: 2345 mm

Economy
Currency: Singapore Dollars (S$1.79:US$1)
GDP: US$87 billion/S$155.7 billion
Per Capita GDP: US$20920
Unemployment 4.2%

Changi Airport control tower.

Manufacturing output from the sector demonstrated 58 % growth last year providing a bright spark amidst the global slowdown in the electronics industry. Last December saw a 131% increase in pharmaceutical exports as new plants were set-up to produce higher-value drugs. This helped the Singapore economy register positive growth, reversing the recession experienced in 2001. And, in a year of overall rising unemployment, the industry created about 1,040 jobs, representing a 136% increase over the previous year.

The pharmaceutical industry in Singapore may have had its beginnings all the way back in the 1970s, but the past five years have seen it being thrust into the limelight as the island-state seeks to become a global Biomedical Sciences hub in Asia. Today, the pharmaceuticals sector is a $4.4 billion industry in Singapore with a strong critical mass of leading international companies.

Quality manpower, good infrastructure, global market networks, and strong intellectual property rights protection have led companies like Aventis, GlaxoSmithKline (GSK), Merck Sharp & Dohme, Schering-Plough, Pfizer, and Wyeth to invest more than $2.4 billion in manufacturing facilities here to produce Active Pharmaceutical Ingredients (APIs) and finished products for global markets. With a steady pipeline of manufacturing investments by leading pharmaceutical players, Singapore is rapidly growing from strength to strength in its status as a key manufacturing launch pad for the global pharmaceutical market.

For instance, Schering-Plough officially opened its new $100 million Biotech Sterile Manufacturing Facility and $78 million Tablet Facility last November. These two facilities will complement its international product manufacturing operations to meet increasing global demand. Schering-Plough also announced that it would invest a further $200 million to build a third multipurpose plant with commercial production from 2005. With this third plant, Schering-Plough's total investment commitments in Singapore would exceed $1 billion and total staff strength would reach 800.

The Manufacturing Hub: Tuas Biomedical Park

The majority of the industry's manufacturing plants are located at the western end of the island at a specially designated area called the Tuas Biomedical Park. Its origins may be traced back to the mid-1990s when the Singapore government allocated a 50 hectare site at Tuas, the industrial hub of the country, as a pharmaceutical manufacturing zone, known then as the Pharma Zone.

It has to date proved successful in establishing a cluster of leading foreign companies such as Pfizer, Wyeth, and Merck, and has expanded into 170 hectares of prepared land for the further clustering of pharmaceutical and biotech manufacturing operations and other shared services.

Excellent infrastructures of roads, sewer lines, and drainage systems have been put in place. There also are future initiatives to provide third party services such as a centralized waste treatment and utility plant for the pharmaceutical facilities there. Due to strong demand, an additional 150 hectares has been developed.

Ingredients for Pharmaceutical Boost - Right Infrastructure and Capabilities

While the tremendous progress of the pharmaceutical industry in Singapore may appear to be an overnight success, in reality Singapore has devoted considerable effort toward developing the right infrastructure and capabilities for this industry to flourish. These include creating plug and play environments for R&D and manufacturing activities as well as providing a strategic mix of financial incentives and grants for R&D and manpower training to help companies jumpstart their operations.

Indeed, the pharmaceutical industry in Singapore has a 30-year history - the first players actually arriving on the island as far back as 1973. In that year, SmithKline started the ball rolling with its antibiotics plant. Glaxo then started its operations in 1979 when it built its first active ingredients plant – a $150 million chemicals plant.

While both companies raised their fixed asset investments in Singapore, they remained very much the only players in Singapore for another 14 years before Fisons opened its chemical plant in 1993.

And in 1997, US-based Schering-Plough set up a $260 million multipurpose chemical plant, which opened the flood-gates for many other US drug companies to bring in their manufacturing operations to Singapore.

Beyond Manufacturing: R&D

In an industry where Research and Development (R&D) is critical to long-term sustainability, many companies, such as Novartis, Eli Lilly, and Bristol-Myers Squibb have invested in R&D activities ranging from basic research to clinical development, attracted by Singapore's multi-ethnic population, well-developed clinical and regulatory infrastructure, strong IP framework, easy access to regional patients as well as strict adherence to international clinical standards.

Some, like GSK and Schering-Plough, have augmented their manufacturing operations in Singapore by building capabilities in process development. Schering-Plough's Chemical R&D Center, which was recently completed, will carry out process development and process optimization activities.

In addition, pharmaceutical companies have broadened the scope of their clinical research activities in Singapore to include early phase trials. In March 2001, Pharmacia established a 24-bed clinical pharmacology center at Singapore General Hospital. It is the second company after Eli Lilly to invest in clinical pharmacology facilities with Singapore's hospitals.

Eli Lilly also launched its corporate R&D center last year dedicated to systems biology research. This is the first major commitment made by any pharmaceutical company in the field of systems biology with the specific purpose of accelerating the drug discovery process. With a $140 million R&D budget over five years, Eli Lilly will employ approximately 50 scientists and information technology professionals.

And taking advantage of Singapore's tropical location, Novartis is setting up a research center to find new drugs and treatments for tropical diseases, initially focusing on tuberculosis and dengue fever.

Apart from the multi-national firms, local firms also have made significant progress in 2002. One such example is home-grown biotechnology firm - MerLion Pharmaceuticals, formed only in July last year, which has successfully raised $13.5 million in equity funding despite a tough global financing environment, and secured collaborations with Abbott Laboratories,

Tuas Biomedical Park is located at the west end of Singapore.

Athelas, Fujisawa, Genome Therapeutics, KuDOS Pharmaceuticals, and Merck & Co. Boasting one of the world's largest and most diverse natural products libraries derived from bacterial, fungal, plant, and marine organisms, the company is looking for active molecules from natural products that work against diseases like cancer and diabetes.

R&D City: Biopolis

Singapore is building a dedicated biomedical research park, known as "Biopolis," to house BMRC's five biomedical research institutions as well as R&D laboratories of pharmaceutical and biotechnology companies. Targeted to start operating from mid 2003 onward, the 2 million square foot R&D complex will incorporate facilities tailored for the Biomedical Sciences, including laboratory space for private biomedical companies, incubators to nurture start-up companies, animal handling facilities, as well as laboratory support services. Central facilities such as shared R&D facilities, auditorium, and lifestyle amenities also will be easily accessible and available to the tenants at Biopolis.

Located near the National University of Singapore, National University Hospital, and the Singapore Science Parks, Biopolis aims to be a breeding ground for synergy and collaboration of new research discoveries between the public and private sector researchers.

Mr Philip Yeo, Chairman of A*STAR as well as Co-Chairman of EDB, highlighted: "Biopolis will be a vibrant community of Human, Intellectual, and Industrial Capital, with leading scientists and top-rate organizations from all parts of the world congregating at a focal point for cutting-edge research. Researchers will be able to interact and exchange ideas, collaborate, and leverage on the different strengths available in both the public research institutes and the private companies."

The Future and Getting There

Moving forward, Singapore is on track to achieving its target of $6.7 billion in Biomedical Sciences manufacturing output by 2005, according to Philip Yeo.

And not only will output continue to grow in volume, the range of activities undertaken by the industry is expected to expand further in terms of the breadth and depth of its manufacturing base. In particular, biologics manufacturing - the large-scale production of protein-based drugs - is likely to increase its presence here as such drugs are expected to account for 50 to 60% of new drugs in the future.

A-Bio Pharmaceuticals, a start-up contract biologics manufacturer will target leading pharmaceutical and biotechnology companies to provide contract manufacturing services, specializing in mammalian cell culture. Its proposed manufacturing plant in the Tuas Biomedical Park is expected to be ready by 2007.

Building Human Capital

To meet the growing need for skills and knowledge in both the manufacturing and R&D segments of the industry, Singapore is trying to attract scientific and technical expertise from around the globe. In addition to the country being a cosmopolitan place to live - with its high public safety, cleanliness, excellent public transport, and English-speaking community - research fellowships and grants are being provided to specialists in the biomedical field.

R&D City: Biopolis.

Singapore Fact Sheet (2002):

Living in Singapore
Literacy Rate: 93.7%
Life Expectancy: 78.7 years
Home Ownership: 93.6%
Population Density: 6055 per sq km

Official Languages:
English (for administration), Chinese, Malay, Tamil

Ethnic Composition:
Chinese: 76.5%
Malays: 13.8%
Indians: 8.1%
Others: 1.6%

At the same time, Singapore is aggressively building its own pool of local talent by strengthening the curriculum for the Biomedical Sciences at all levels.

The Ministry of Education has modified the country's primary and secondary school curriculum to provide foundational understanding of the Biomedical Sciences as well as basic training in modern scientific investigative skills.

At the post-secondary level, all four of Singapore's polytechnics, which provide tertiary-level vocational training, are now offering courses for biomedical lab technicians and research assistants. And at the university level, the National University of Singapore revamped its life sciences curriculum last year to put greater emphasis on research. The country's other university, the Nanyang Technological University, has recently established its School of Biological Sciences and had its first intake of 100 students in July last year.

Various scholarships for both undergraduate and postgraduate degrees also have been set up. A*STAR's National Science Scholarships, which was launched in 2001, will support undergraduate and postgraduate training up to PhD and postdoctoral level for about 600 research scientists in the Biomedical Sciences.

And to ensure that training is not restricted to theory, the EDB also has developed an industrial training program for biopharmaceuticals manufacturing. Under the Training and Attachment Programme (TAP), engineers and scientists will be sent for a period of between 12 and 18 months to leading companies in Europe and US where they will be trained in the areas of process development, validation, and quality assurance.

Protecting Intellectual Property

To further encourage researchers to create intellectual property on the island, the Intellectual Property Office of Singapore was launched in 2001 to provide the infrastructure, platform, and environment for greater creation, protection, and exploitation of intellectual property.

Singapore has achieved full compliance with the World Trade Organization's Trade-Related Aspects of Intellectual Property Rights Agreement one year before the 2000 deadline. It also has been ranked by the Political and Economic Risk Consultancy as having the best intellectual property rights protection in Asia since 1997. Singapore is also a signatory to the World Intellectual Property Organization, the Paris Convention, the Budapest Treaty, and the Patent Cooperation Treaty. The Health Sciences Authority under Singapore's Ministry of Health also provides a comprehensive regulatory framework for the evaluation and marketing approval of all therapeutic products.

On Target

Since the launch of the Biomedical Sciences initiative in June 2000, Singapore has successfully built a growing reputation in the international biomedical community for its comprehensive plans, stringent IP protection, and strong commitment to develop the Biomedical Sciences cluster. Its success in both manufacturing and R&D are a clear signal that the island-state has the right mix of public research and industry involvement for the high value-added and technology-intensive Biomedical Sciences cluster.

The Regulatory System of Singapore

by Dr. Clarence Tan, Chief Executive Officer, Health Sciences Authority

Singapore's Regulatory and Industry Development

In the 1960s, the pharmaceutical manufacturing industry in Singapore comprised mainly the local generic manufacturers and Singapore had no regulatory GMP audit program then. It was not until 1973 that Beecham Pharmaceuticals, a UK-based company, became the first Multi-National Company (MNC) manufacturer to set up a plant in Singapore to manufacture bulk semi-synthetic penicillins.

Today, there are at least 10 MNC pharmaceutical manufacturing facilities in Singapore, including Schering-Plough, GlaxoSmith Kline, Aventis-Pharma, Wyeth Pharmaceuticals, Merck, Pfizer, and Baxter Healthcare.

Following the closure of the Government Production Laboratories in 1986, the licensing of pharmaceutical manufacturers and the registration of medicinal products commenced the following year under the framework of the Medicines Act.

A GMP Unit was established in 1997 within the Ministry of Health (MOH) to deal with the increasing types and number of manufacturers, and to manage the increasing specialization in the field of GMP. The licensing of Chinese Proprietary Medicine (CPM) also began in 1999.

More recently, on 1 April 2001, the Health Sciences Authority (HSA) was established as a statutory board of MOH. HSA comprises

Singapore Health Sciences Authority building.

eight professional centers, including the Centre for Pharmaceutical Administration (CPA), which administers the regulation of drugs and health-related products. The other professional centers include the Centre for Analytical Science (CAS), Centre for Drug Evaluation (CDE) Centre for Forensic Medicine (CFM), Centre for Forensic Science (CFS), Centre for Medical Device Regulation (CMDR), Centre for Radiation Protection (CRP), and the Centre for Transfusion Medicine (CTM).

CPA has four divisions, namely the Manufacturing and Quality Audit (upgraded from GMP Unit), the Product Evaluation and Registration, the Compliance and Complementary Medicine, and the Pharmacovigilance, Communications and Research Divisions.

The Manufacturing and Quality Audit arm of CPA comprises three Units, namely the GMP Audit Unit, the GDP Audit Unit, and the Certification Unit.

- The principal functions of the GMP Unit include the audit and licensing of manufacturers of sterile and non-sterile medicinal products, CPM, cosmetics, as well as CLS.
- The principal function of the GDP Unit is the audit and licensing of importers, wholesale dealers, and the retail and hospital pharmacies.
- The Certification Unit processes and grants various certificates such as the Certificate of a Pharmaceutical Product and Certificate of Licensing Status (under the WHO Certification Scheme), the Free Sales Certificate and other Export Certificates, as well as GMP certificates

Accession of Singapore to the Pharmaceutical Inspection Co-operation Scheme (PIC/S)

In line with the national goal of Singapore to be a life sciences hub, the GMP Unit embarked on a quality journey to benchmark itself against overseas centers of excellence in the field of GMP audit and licensing of pharmaceutical manu-

facturers. In July 1997, a formal application to accede to PIC/S was submitted.

PIC/S comprise countries with equivalent high standards of GMP inspection system, and include the European Union countries, Switzerland, Australia, and Canada. Two PIC/S delegations visited Singapore in April 1999 and November 1999 respectively to assess its system of GMP inspection and licensing of pharmaceutical manufacturers. The PIC/S delegations concluded that the Singapore system of GMP inspection and licensing can now be considered to be "equivalent to that of PIC/S member authorities, and Singapore has set a benchmark for other GMP inspectorates in the region to match." *With effect from 1 January 2000, Singapore became the first Asian country to accede to PIC/S.*

With HSA's membership of PIC/S, Singapore is now in a position to pursue Mutual Recognition Agreements (MRAs) with other PIC/S countries, beginning with Australia. An MRA on GMP Inspection was signed between the Governments of Singapore and Australia on 26 February 2001. The signing of this MRA means that the Therapeutic Goods Administration (TGA) of Australia now accepts the GMP audit reports and the conclusions of the GMP Auditors of HSA and vice-versa.

Singapore and Japan also have signed an Economic Partnership Agreement on 13 January 2002, which also included a Joint Statement on Pharmaceutical GMP Inspection, which provides for the exchange of GMP audit reports between Singapore HSA and the Japanese Ministry of Health, Labour, and Welfare (MHLW).

With these developments, the status of Singapore as a regional life sciences and pharmaceutical hub has been enhanced considerably.

The GMP Audit System of Singapore

The GMP inspection system of Singapore follows closely the international practice of PIC/S. The risk assessment approach for determining the frequency of GMP audits is used.

For finished dosage forms, Singapore has adopted the PIC/S GMP Guide for Medicinal Products as its GMP standard. In the case of Active Pharmaceutical Ingredients (APIs), the PIC/S GMP Guide for API (equivalent to the International Conference on Harmonization Q7A Guidelines) has been adopted by Singapore as the corresponding standard.

Licensing of Pharmaceutical Manufacturers in Singapore

The Medicines Act of Singapore states that no person shall manufacture or assemble any registered medicinal product unless he has a manufacturer's license, and the licensing authority shall take into consideration the following criteria before granting a Manufacturer's License:

- proposed manufacturing operations
- details of the premises
- equipment used for manufacturing and QC
- qualifications of key personnel
- Security of the premises and the maintenance of adequate written procedures and records

Standard Provisions for a Manufacturer's License

The standard conditions or provisions for a manufacturer's license are set out in the Fourth Schedule to the Medicines (Licensing, Standard Provisions, and Fees) Regu-

lations. The holder of a Manufacturer's License must comply with the specified provisions, which includes complying with the PIC/S Guide to GMP for Medicinal Products, as revised or amended from time to time.

Strategic Directions and Challenges

HSA will continue with its domestic program to internationalize the local pharmaceutical manufacturing industry standards, in particular the generic product suppliers and the manufacturers of CPM.

Seminars and workshops will continue to be organized on quality topics. The risk-based GMP audit program will continue, and where necessary, the appropriate regulatory actions taken against recalcitrant companies and non-conforming manufacturers.

In the near future, HSA also will have to pay attention to new categories of products such as biotechnology products, new types of APIs, clinical trial products, and health supplements. It is very likely that HSA will participate more actively in international harmonization of GMP standards and audit systems through PIC/S.

More bilateral government-to-government MRAs on GMP inspection, which will result in greater industry benefits, are expected to be negotiated and signed. An overseas GMP audit program involving more than 1000 overseas manufacturers also is expected to be implemented soon.

Questions relating to the article may be directed to:
Manufacturing and Quality Audit Division
Centre for Pharmaceutical Administration
Health Sciences Authority Singapore
Email: sia_chong_hock@hsa.gov.sg
Web site: www.hsa.gov.sg

R&D In Singapore: A New Challenge

A personal perspective from Dr. Miranda Yap,
Director of Bioprocessing Technology Centre, Professor of
National University of Singapore (NUS), Department of
Chemical and Environmental Engineering

The Early Days

Dr. Miranda Yap is a Director of one of Singapore's public research institutes - the Bioprocessing Technology Centre (BTC) - and is considered by many to be a pioneer in the nation's burgeoning biomedical sciences research efforts. Her interest in bioprocess science and technology was kindled while she was pursuing a Master's degree in biochemical engineering at University College London in 1973, after earning her basic degree in applied chemistry from the National University of Singapore (NUS), then known as the University of Singapore.

Following her Master's degree, she joined Singapore Petroleum Company, a local oil refinery, as a chemical engineer just as many of her peers were working for the oil and gas industry, which was booming in Singapore during the 1970s.

Recalls Dr. Yap: "Many of my undergraduate classmates worked for petroleum companies and upon retirement, were given great golden handshakes! But candidly, I found such a 'regular' job rather stifling."

And so in 1975, she embarked on a doctorate program in chemical engineering at the University of Toronto. After earning her PhD in four years, Dr. Yap spent another three years in the United States conducting postdoctoral research. But even as career opportunities abound for her in the North Ameri-
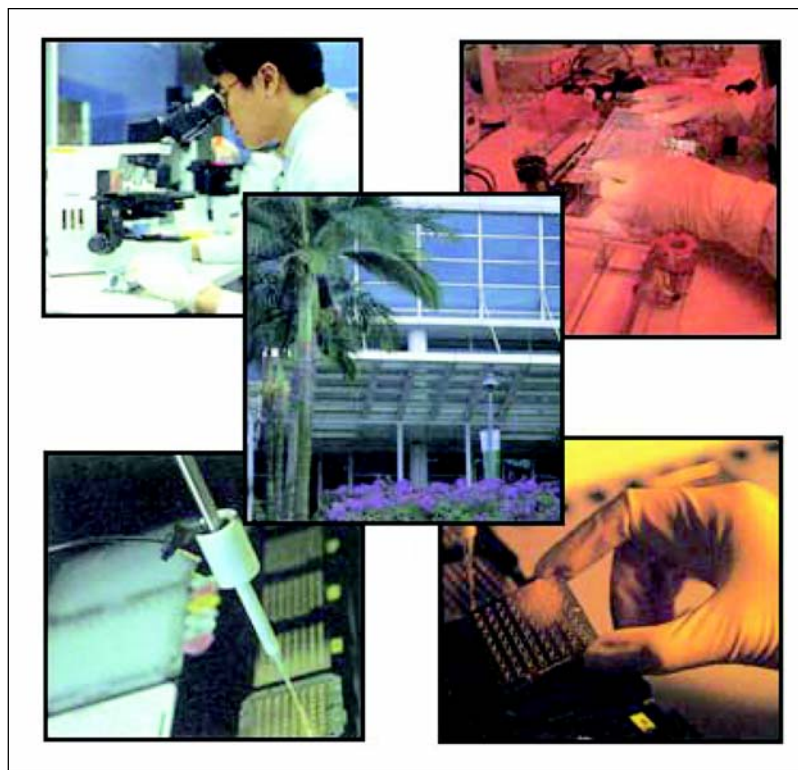
Bioprocessing Technology Centre Building (BTC).

can continent, her heart yearned for home and her family. In 1982, she returned to Singapore and joined NUS.

"I recall that as an undergraduate I was always harboring thoughts of a teaching career in NUS," she says, "So in 1982, my husband and I made a conscious choice to return to Singapore."

Fortunately for her, the early 1980s were a good time for academics to return to Singapore. Research money was readily available as the Government was then seeking to build up the nation's local universities. In addition to ample funding, researchers also were given relatively free reign in defining their research areas, she says. But even with the early support of the Government, Dr. Yap's journey into research was not an entirely smooth one.

Bioprocessing Technology Centre (BTC) and Manpower Training

As Dr. Yap continued in her academic career over the next few years, the government soon identified a need to initiate manpower training in the area of bioprocess technology as it sought to attract and anchor biopharmaceutical companies to Singapore in a bid to

Institute of Molecular and Cell Biology Building (IMCB).

expand the island's manufacturing base.

A task force comprising of NUS faculty from various departments and industry representatives was set up to look into establishing a center, which would complement the upstream activities of the Institute of Molecular and Cell Biology. The IMCB had been set up in 1987 and was Singapore's first public biomedical sciences research institute, focusing on basic research in molecular genetics, including cell regulation, cell cycle control, and genomics.

Being a member of the task force, Dr. Yap was instrumental to the formation of the Bioprocessing Technology Unit (BTU). Her proposal to initiate the unit in NUS' Chemical Engineering department was accepted in 1990 and the BTU was born with a $6 million grant from the Singapore Government and 3,000 sq feet of laboratory floor space. The BTU was subsequently renamed the BTC and took on the additional role of a national R&D center, with funding from Singapore's National Science and Technology Board.

In starting up the BTC, the main challenge that Dr. Yap faced was the sourcing for experienced senior scientists. At that time, bioprocessing technology was still a nascent research area in Singapore, and so it was difficult to attract the right people then, she recalls. Nonetheless, she eventu-

ally managed to find enough senior scientists from overseas and bright local graduates also helped to fill places as they became attracted to new career choices in the biopharmaceutical sector.

Today, the BTC continues to play a pivotal role in manpower training with core strengths in expression engineering, animal cell culture, downstream purification, and analytics focused on enhancing product yields and quality.

Biomedical Research Council (BMRC)

Together with the IMCB and three other research institutes - the Genome Institute of Singapore, the BioInformatics Institute, and the Institute of Bioengineering and Nanotechnology, the BTC is one of the five pillars of Singapore's Biomedical Research Council (BMRC), which was established in October 2000 to coordinate and support biomedical research in the public sector. Apart from funding public biomedical research initiatives, the BMRC's other role is to build up a talented pool of biomedical researchers in Singapore. It has established several manpower development initiatives that include scholarships and exchange programs.

Next up, the BMRC will be moving its member research institutes into a new dedicated biomedical research park called "Biopolis." The 194 hectare research center, which is expected to be completed in June 2003, will house all of BMRC's R&D activities from basic drug

discovery research to clinical development to medical devices research. Sited near NUS, hospitals and other research institutes, the BMRC research arms hoped to seed a vibrant research community by attracting private industry research from both multi-national drug firms and local biotechnology start-up companies.

Indeed, the story of biomedical sciences research in Singapore would not be complete without acknowledging the growing number of leading pharmaceutical companies, which have set up R&D operations on the island.

For example, Eli Lilly recently established its state-of-the-art center for systems biology, its first outside of the US to look into the development of computational tools for drug discovery.

Local start-up companies also have not been left out of the fray. These include ES Cell International - a stem cell company - that arose from research done at NUS, Monash Institute of Reproduction in Australia and Development and Hadassit Medical Research Services and Development in Israel.

As Dr. Yap aptly sums it up, "Research is more than just a passing fancy, but is a life line for Singapore. This is because there is a great need to couple manufacturing and R&D in high knowledge-based industries.

"The key attractions for such companies to locate here for manufacturing are the availability of a highly qualified manpower pool and relevant technologies which will add value to the industry.

"Thus, it is critical to meet these needs through the research institutes and universities to build up relevant manpower and technologies to attract them."

A Thriving Biomedical Sciences Industry

by Ms. Chu Swee Yeok, Director of the Biomedical Sciences Group; Executive Director of the Biomedical Sciences Investment Fund, Singapore Economic Development Board (EDB)

Singapore is positioned as the choice location for global manufacturing, supply chain management, distribution, as well as upstream activities including process development, clinical development, and R&D for Biomedical Sciences. In close partnership with industry, EDB's Biomedical Sciences Group (BMSG) focuses on broadening and diversifying the range of Biomedical Sciences activities in Singapore and ensuring that a sound supporting infrastructure is in place.

Over the years, Singapore's base of pharmaceutical manufacturing activities has expanded from primary manufacturing by companies such as Aventis and GlaxoSmithKline to include secondary manufacturing such as tabletting, formulation and finishing by Merck and Wyeth, and nutritionals manufacturing by Wyeth. Schering-Plough also has added biotechnology lyophilization into Singapore's host of high value-added manufacturing activities. Singapore's ability to extensively support production and manage the supply chain of high-value pharmaceutical products to the global markets through its excellent infrastructure, strong IP framework, and availability of skilled manpower has been strengthened through the breadth and depth of such manufacturing activities.

Promising growth areas such as the biopharmaceuticals sector will continue to be nurtured as Singapore extends its BMS industry capabilities. The recent opening of the small-scale $19 million cGMP facility of the Biopharmaceutical Manufacturing Technology Centre will introduce clinical-grade biologic manufacturing capabilities for the production of monoclonal antibodies and other biopharmaceuticals.

Singapore is also an attractive and strategic location for companies to conduct and manage clinical development activities in Asia. Pharmaceutical companies like Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Merck Sharp and Dohme, and Novo Nordisk base their clinical development teams in Singapore to oversee clinical trials in the region. Success factors include Singapore's multi-ethnic population, well-developed clinical and regulatory infrastructure, easy access to regional patients, as well as strict adherence to international clinical standards. These companies work closely with the local hospitals and Contract Research Organizations (CROs) such as Covance, Icon, and Quintiles to conduct early to late stage trials in Singapore and in the region. Such developments are further bolstered on the regulatory front, where the Health Sciences Authority (HSA) under Singapore's Ministry of Health ensures that there is a strong regulatory framework that is supportive of clinical research.

Apart from manufacturing and clinical development, the Singapore government has been nurturing the growth of a critical mass of companies undertaking R&D in Singapore. In 2000, a $600 million fund was introduced to encourage companies to establish their R&D centers or spin-off research projects. This has attracted large pharmaceutical and smaller biotechnology companies to undertake R&D in Singapore, including Novartis, Eli Lilly, Pharmalogicals Research (a joint-venture between Chugai Pharmaceuticals and Mitsui & Co), and Agenica.

To further facilitate the growth of Biomedical Sciences companies with innovative technologies, EDB has set up Bio*1 Capital to manage a $600 million BioMedical Sciences Investment Fund (BMSIF) and other Biomedical Sciences funds. Bio*1 Capital plays a key role in investing in selective companies, commercializing indigenous technolo-

- Global Manufacturing Base
- Regional Hub for Clinical Development
- Vibrant Environment for New Ventures
- Strong IP Rights Protection
- World-Class Infrastructure

Singapore - Best for Business
- Best Asian City for Business - EU 2002
- Tops in Physical Infrastructure - PERC 2002
- 1st in Asia in Entrepreneurial Framework - EIU Report
- 2nd in Economic Freedom - Washington based Cato Institute 2002
- No. 1 in Labor Force Evaluation Measure - BERI Report 2001
- 3rd Most IT Savvy Nation - World Economic Forum 2003

Sectors	Employment		
	2001	2002ᴾ	% Growth
BMS Total	6,477	7,177	10.8%
Pharmaceuticals	2,375	3,123	31.5%
Medical Technology	4,102	4,054	(1.2%)

2002 Pharmaceuticals Employment (Source: Singapore Economic Development Board).[P = Projected]

| Manufacturing	Value Added ($ million)		
	2001	2002	% Growth
Biomedical Sciences	2,131	3,746	76
Pharmaceuticals	1,613	3,157	96
Medical Technology	517	589	14
*All figures are based on EDB's preliminary estimates.			

2002 Industry Performance: Value-Added (Source: Singapore Economic Development Board).

gies from local universities, or forming strategic joint ventures entities in Singapore. To date, it has invested its funds in more than 80 companies in Singapore as well as overseas.

In addition, other programs have been initiated to promote and commercialize indigenous technologies in the Biomedical Sciences. These include the EDB SEEDS (Startup EnterprisE Development Scheme) program which provides matching equity funds of up to $160,000 for start-ups in the seed stage of enterprise formation, and the Biomedical Sciences Innovate 'N Create Scheme (BMS INC) under Bio*1 Capital, which provides start-up funding specifically to viable business ideas in the Biomedical Sciences. Under the BMS INC scheme, qualifying companies are eligible to receive up to $1.1 million of seed capital.

At present, Singapore is home to some 30 biotechnology companies, including international companies like ViaCell and Proligo, as well as a growing number of local start-ups such as S*BIO, CordLife, ES Cell International, and MerLion Pharmaceuticals. This growing pool of both local and international biotechnology companies involved in drug discovery and development clearly reflects Singapore's attractiveness and growth potential as an excellent breeding ground for new research discoveries to take off.

Comprehensive infrastructural support is aggressively being put in place for the BMS sector as well. Expansion of prepared land for manufacturing in the Tuas Biomedical Park, and a fully integrated R&D complex at Biopolis, which can house more than 2,000 scientists promotes physical clustering. This allows for economies of scale and significant savings through shared services and collaboration.
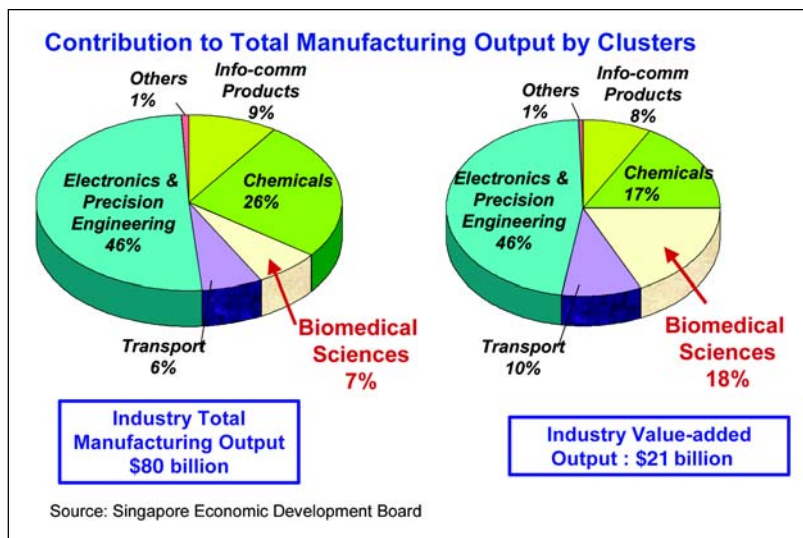
2002 Industry Performance: Investment Commitments.

Singapore - Valued Partner for the Long Term

Within a relatively short span of time, Singapore has demonstrated significant progress and is on track to achieving its target manufacturing output of $6.7 billion by 2005. The government is committed to the Biomedical Sciences sector, and will continue to actively provide a sound investment climate, a pro-business and vibrant research environment for leading biomedical companies and talents to set up base in Singapore.

This article presents an Electronic Validation (eValid) project initiated by a research group at the University of Manchester Institute of Science and Technology (UMIST).

An Information Based Approach to Validation

by Hosam Aleem, Stuart Lord, Tim McCarthy, Paul Sharratt, and Yuyang Zhao

Introduction

Validation is a key component of Good Manufacturing Practice (GMP) in the pharmaceutical industry. In addition to being a regulatory requirement, it also makes good business and technical sense. While the importance of the concept of validation is evident, the practice is problematic. This has prompted a research group at the University of Manchester Institute of Science and Technology (UMIST) in the UK to investigate this problem. This is taking place through the Electronic Validation (eValid) project funded by the Engineering and Physical Sciences Research Council (EPSRC) in the UK under the Innovative Manufacturing Initiative (IMI).

The objective is to approach validation in a structured and formal way in order to analyze it and propose solutions aimed at improving its practice and better integrating it into the overall business process. It is also intended to quantify the benefits gained from applying this methodology.

The eValid project is proposing a novel methodology that relies on emerging IT standards. The idea is to make the most use of the information already available early on in the project lifecycle. This information is increasingly in electronic form, employing such standards will facilitate performing a large percentage of the validation tasks electronically, or eValid. Work is currently under way, and a demonstrator implementation is expected to be ready by mid-

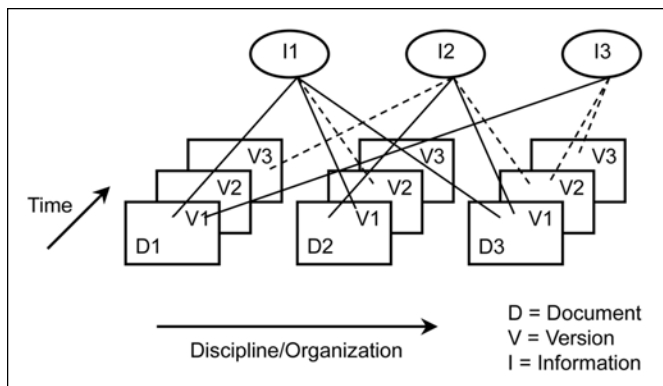Figure 1. A sample business information model of validation.
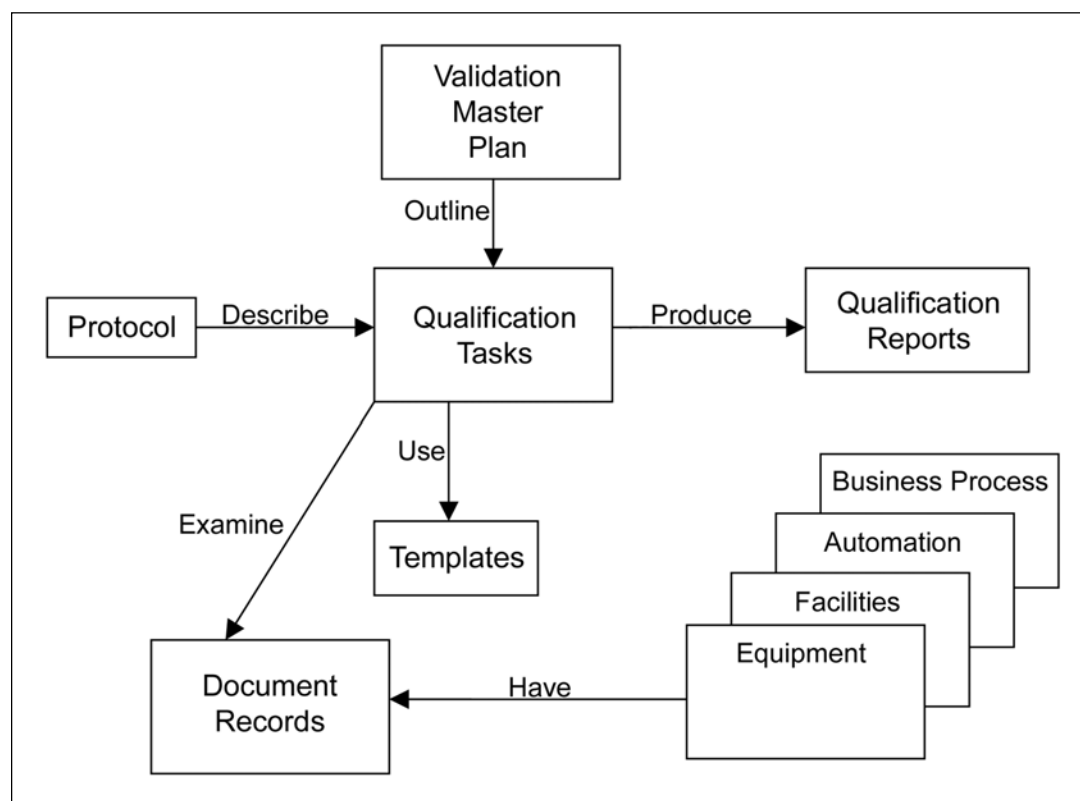
Figure 2. Document content map.

2003. The department of Civil and Construction Engineering and the department of Chemical Engineering at UMIST are both involved in this research. The former has a Project Management division, and several staff members with strong interest in IT and Computer Aided Engineering (CAE), while the latter is interested in manufacturing processes that include pharmaceuticals and biotechnology. Industrial collaborators include major pharmaceutical manufacturers, contractors to the pharmaceutical industry, and software developers and suppliers.

The purpose of this article is to inform the practicing pharmaceutical community of the project's goals and to invite feedback and comments.

Problems with Validation

In the years since its introduction, several developments have occurred in the practice of validation, but also several problems became evident. The prominent ones are summarized below.

- The scope of validation is still not clear. The question "How much validation is enough?" doesn't have a definite objective answer.
- There is significant duplication of effort throughout the life cycle of a project. Many tasks, tests, and inspections carried out during installation, commissioning, and start-up/handover are repeated again in qualification.
- A large volume of paperwork is generated by the validation activity. Validation has become effectively a paper chase.

The approach taken by eValid to address the problems with validation focuses on item three above. It proposes moving from a document-based paradigm to an information-based one. It further claims that this step will significantly reduce the duplication of tasks involved in validation. In addition, it is believed that this new paradigm, coupled with other techniques to be mentioned later, will lead to a more objective decision on the problem of scope. It is interesting to note that the problem of documentation is to a great extent caused by the other two problems. Indeed, the lack of consensus on the scope and requirements of validation leads to an attitude of "better be safe than sorry," causing more - possibly unneces-

sary - validation work to be done. Similarly, the duplication of tasks generates even more paperwork. Yet, solving the problem of documentation will contribute to solving the other two.

Below we give highlights of the eValid approach, and discuss how it relates to each of the above problems. In what follows, validation is discussed as it relates to engineering activities, i.e., qualification of facilities, equipment, and automation rather than in cleaning validation or analytical method validation.

Validation: A Paper Chase

The approach taken by eValid is based on the fact that a large percentage of the documents - or more precisely information – needed in validation is generated during the earlier phases of the project. These include the design, construction, and commissioning phases in addition to product and process development activities where the product characteristics and process conditions are specified. Example documents (information) include requirements specifications, design and construction drawings, material and personnel certificates (e.g. welding and welders), data sheets, operating procedures, manuals, test and inspection reports, etc. Thus, there is a large pool of information and documents from which most of the validation activities will choose, examine, and verify, and which is already available, albeit in a non-homogeneous form - *Figure 1*.

Traditionally, this vast amount of documents has been managed and controlled through some document management system. To keep matters under control, strict change control procedures are implemented that encompass detailed provisions for initiating, evaluating, reviewing, and approving the proposed changes. Nevertheless, a problem of content consistency is bound to appear at some point in time, because some of the document content is likely to appear in other documents which may have been created in other organizations at different points in time - *Figure 2*. When there are many such documents, it becomes exceedingly difficult to maintain an accurate map of this shared content, let alone maintain its consistency across changes, even in the presence of a strict change control process. The document change control process places greater emphasis on maintaining the evolution of a given document under control, rather than how changes in this document relate to and indeed affect other documents, i.e., traceability between documents.

It becomes clear that an alternative view of documentation is needed. This approach will totally eliminate documents and take an information based approach. This might appear surprising given that documents have long been regarded as the repositories for information. Indeed, in the pharmaceutical industry if something is not recorded, then it hasn't been done. However, no claim is made to depart from the practice of recording, it is just the concept is now viewed differently where the information based approach replaces the master role of documents with electronic records. Documents will still be available, but are just a snapshot of a particular collection of information at a particular point in time. What is needed is a more abstract look at the FDA's

definition of validation, repeated below from its guideline document on process validation.[1]

> *"Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics."*

The issue here is that *"documented evidence"* is frequently interpreted as documentary evidence, and thus most of the legacy documented evidence is taken to be paper documents. However, a document is a set of information. The document itself will have a format or presentation structure, but the content of the document (what the document is about) may vary from highly structured, like a data sheet which is a set of items (objects or classes) in a table for instance, to unstructured such as free text or an image. Thus, the problem of content consistency mentioned above becomes even more evident. Note that merely moving from a paper based document paradigm to an electronic one will not solve the problems inherent in document content management if this move is not coupled with a change in philosophy. Granted, the electronic domain will provide more document management functionality, but it does not necessarily solve the information consistency problem. However, it is a step in the direction of solving this problem, when coupled with means to embed the meaning of the content within the electronic document itself. Indeed, an electronic document may be more or less 'intelligent' depending on whether the meaning of the content is explicit in its structure or not. An example of a 'dumb' electronic document is a fax, which is just a bitmap, i.e., a collection of dots on paper, which doesn't say much about the content unless interpreted by a human or an Optical Character Recognition (OCR) system.

In order to solve the document content consistency problem, one should manage at the individual information item level. This requires an identified owner and change management procedure for individual information items and definition of their meanings. Thus, when each information item is controlled, it doesn't matter in how many documents it will appear as it will always be the same version. The next issue then would be how to structure and represent this information such that it can be understood by the different systems in which it will be needed.

In most modern facility construction activities, an increasing percentage of the calculations, drawings, and documents created in the design, construction, and commissioning phases of the project are in electronic form. However, these electronic forms are mostly different and possibly incompatible. Indeed, the software used by the design organization for example, may be different from that used by the construction organization, consultant, supplier, or regulatory authority, even if some of these software products perform the same functions. In addition, many of these electronic documents will eventually have to be transferred to the owner/operator who may yet have a completely different system - *Figure 3*. Many of the

organizations involved may not necessarily be willing to switch to a software product used by one of the others, as each may have many other customers. Obviously, a supplier cannot change his work system for every customer, especially in the case of minor jobs. The exception would be when there's a strategic partnership between the supplier and the customer, or in the case of suppliers who have multiple systems, and those would probably be larger organizations.

In order to be able to achieve seamless transfer between different heterogeneous IT systems, two issues need to be addressed: the meaning of the information and its format. These will have to be independent of any software application, thus enabling sharing with even yet unknown users. Indeed, this is the case at the early stages of a project when no bidding has been assigned, and thus, specific users of the information are yet unknown. One way to achieve this is to utilize emerging standards that define the meaning of information explicitly in its structure. One such standard that has been successfully employed in the oil and gas industry is ISO 15926 with its different parts, titled "Integration of Life Cycle Data for Oil and Gas Production Facilities." In particular, Part 2 deals with the so called "Data Models," and Part 4 is a "Reference Data Library."

As for format, the machine readable language in which the information is expressed has to be defined. This should be a widely accepted international standard that meets the technical requirements. There are several to choose from, and inevitably the choice is not unanimous. The capability to map from one language to another is required. One obvious choice is Extensible Markup Language (XML) in addition to meeting the above requirements, it has a number of other advantages. XML extends HTML capabilities to describe the structure of document content as well as its format. This capability allows documents not only to be displayed on the Web (as with HTML), but also to share its content with other documents and to communicate with other software applications and databases. Other advantages include its widespread and growing use, its applicability to a Web-based environment, and its inherent power and flexibility yet relative simplicity for defining semantics. The development of the XML work done in eValid again follows standards, in this case, those set by the World Wide Web Consortium (W3C).[2]
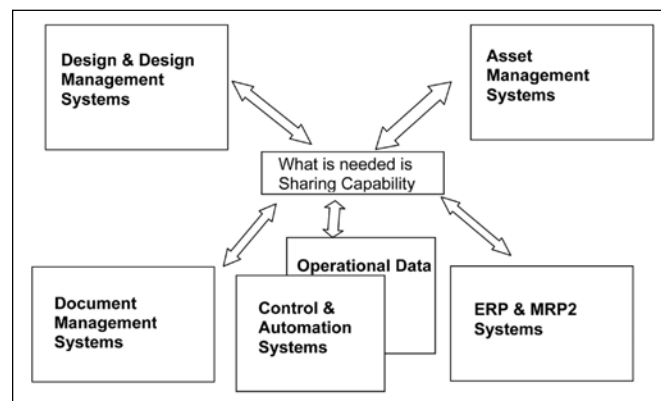

Figure 3. Information sharing across systems with different functionality.

It should be noted that using such standards and indeed enabling the sensible communication of different IT systems is not an aim for its own sake, but a means to achieving the improvement to the validation practice aspired for. Thus, the reader should not lose sight of the ultimate goal in the details of the implementation. In fact, most of these implementation issues will be hidden from the end-user in a real life situation employing this methodology. The end-user here being the user of this information whether for validation or any other activity within the drug manufacturing business process.

We have highlighted above the approach from a practical standpoint and how it relates to the end user. However, there are theoretical issues that aren't covered here such as the formal modelling and analysis of the validation activity and its information requirements within the overall business process. This was the starting point and was performed using process modelling and reengineering tools.

Validation, How Much is Enough?

This question has been debated in industry and the literature for many years, and the answer is highly subjective. There is no consensus on this issue, not even among regulatory inspectors. Indeed, it is possible to have two firms with different extents to which they have validated their processes, yet they both get regulatory approval, implying that one must have done more than is necessary. This leads to a fundamental question concerning the consequences or the costs of over-validation and under-validation, even if the company passes inspection. An even more fundamental question poses itself namely, what is the value added by the validation activity in

the overall context of the business process and how to quantify it? These issues will be considered in more detail later. At this point, we will consider how much is enough and how to determine it.

Resuming our earlier discussion of documents and information, one can take yet another abstract look at the FDA definition of validation and replace the phrase "*documented evidence*" by "*verifiable evidence.*" In the context of the information based electronic paradigm proposed earlier, and in view of the recent regulatory requirements concerning electronic records and electronic signatures as stated in 21 CFR Part 11[3] and elaborated upon in the related recent guidelines,[4] it is evident that electronic records are secure, authorized, and verifiable although they are not necessarily the equivalent of documents. Thus, perhaps the original definition may be expanded to accommodate different approaches, rather than be restricted to documents. After all, the core of the activity is to *verify* or prove the consistency of the performance of the process.

Two other issues need to be resolved concerning verification. First, what needs to be verified? And second, what level of verification is necessary to provide "*a high degree of assurance*?" i.e., an issue of breadth and an issue of depth.

To determine the scope of validation, and thus to answer the question of how much is enough from a breadth perspective, eValid proposes basing the answer on a quantification of the risks associated. The idea of relying on risk assessment is hardly new, and is recommended by ISPE's GAMP 4 in the context of computer validation.[5] However, little seems to have been done in terms of quantifying these risks, even in GAMP 4 where the approach is more qualitative (high,
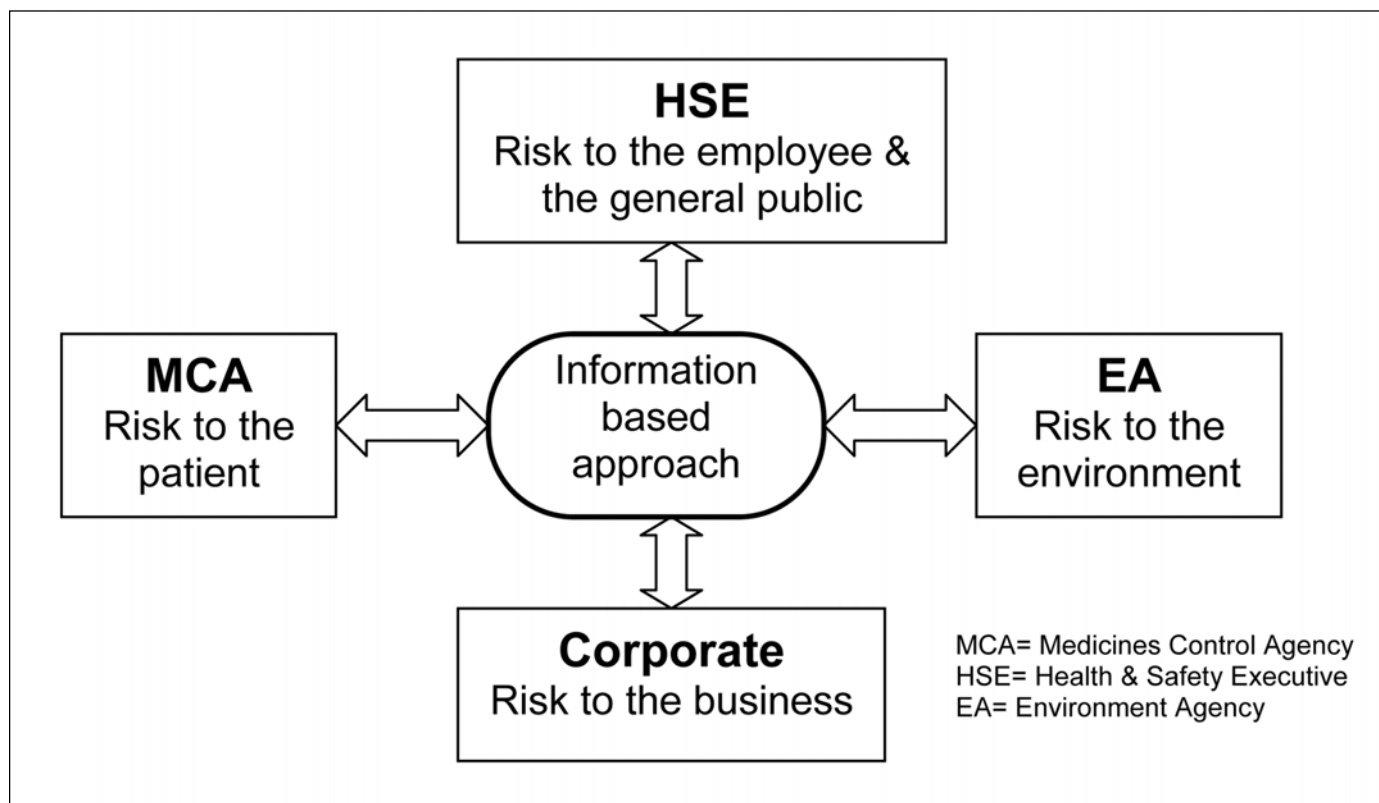

Figure 4. Risks relevant to the business and the regulatory authorities.

medium, and low). It is not claimed that this is an easy task, and will probably eventually have to rely on subjective sources such as the estimates of experienced individuals. Nevertheless, quantification adds a level of objectivity that is hoped to increase as the practice matures. It should be noted at this point that the ISPE Baseline® Guide on Commissioning and Qualification[6] addresses the issue of scope, by calling for impact assessment of the different systems at the onset of the project in order to determine what to be qualified. It is thus a notable contribution toward solving this problem although the practice still needs to be refined.

The context of risk is another area where the information based approach proposed by eValid adds yet more value. While GMP is constrained to risk to the patient from faulty products, risks to the environment, employees, and the general public are excluded. Such risks are still important to the business as well as to other regulatory authorities such as (in the UK) the Environment Agency and the Health and Safety Executive. Risk assessment will rely on information already produced earlier in the project, and which would be readily available, accessible, secure, and verifiable through the above mentioned approach. Indeed such an approach deals with all the information of the project/process/ facility and is not limited to those for validation. Thus, it helps integrate the whole business process, and facilitate fulfilling all regulatory requirements based on such information and not only those for GMP - *Figure 4*.

As for the issue of the level of verification, in addition to being related to risk, it is also related to the nature of what to be verified. This may be a facility, equipment, material, procedure, or personnel. Those terms are used here in a generic sense and some or all of them may constitute a process whether technical or business. In an effort to be more structured in determining the required level of validation and make it more objective, eValid is proposing a classification of the different levels of verification. For instance, for a physical item (material, equipment, facility), one possible approach may include the following levels, where the lower numbers reflect lower levels of verification:

1. Level 1: an item that is a commodity, and thus would require almost no verification.

2. Level 2: items for which the supplier has to demonstrate the implementation of a quality system such as ISO 9000 certification, or by supplying quality records or SPC (statistical process control) charts.

3. Level 3: items for which the supplier would have to supply a certificate, such as a calibration certificate or a legally binding statement of conformance, this level also may involve supplier audit by the customer.

4. Level 4: items for which an independent third party accreditation of the supplier or test of the item is required. This third party may be a regulatory body or a recognized national or international professional body.

Other levels are conceivable. A similar argument can be made for personnel, in which case requirements may include an apprenticeship and/or certain years of experience, an academic degree, or certification by some professional or governmental testing body. The point is that different levels of verification can be associated with the different levels of performance required from the object/person/process. Another dimension of the classification would be related to the context where the item will be employed. Thus, the same class of item will need to be verified to a higher degree if used in manufacturing a sterile product than it would be for an oral dosage form for example. The same concept applies to personnel, even if they have the same set of technical skills. This clearly relates back to the issue of risk.

Eliminate Duplication

As mentioned earlier, many of the activities performed in qualification are a repetition of inspections and tests carried out in the earlier phases of the project. In particular, those activities include construction, commissioning, Factory Acceptance Testing (FAT), and Site Acceptance Testing (SAT). This has been the situation traditionally, more recently however, validation is being taken into consideration early on in project planning and is being integrated with the rest of its activities. One such approach is the current trend toward applying Good Engineering Practice (GEP) in all engineering work, as recommended by the ISPE Baseline® Guide on Commissioning and Qualification, and indeed the whole of the baseline series and other similar good practice guides.

Such good practices producing reliable information, when coupled with the electronic information handling paradigm proposed by eValid making this information reliably accessible and verifiable, can lead to the elimination of much of the duplication currently taking place in qualification activities - *Figure 5*. Indeed, we propose doing away with all the qualification work that duplicates tasks that have been performed in earlier phases of the project, having maintained that it was performed according to good practices, and the information handled appropriately. In such a case, most of IQ and OQ and even some of PQ would become effectively an audit of these activities performed earlier and not a repetition of them. Obviously, some other qualification and validation activities will still have to be done, especially those concerning the actual performance of the process and testing it under the different realistically conceivable operating conditions.

Eliminating this duplication raises an important issue that needs to be addressed, and that is whether the repetition of testing is necessary for validation. This is meant here on a more fundamental level, i.e., is it a requirement in order for the practice to be called validation to begin with, irrespective of whether it is a regulatory requirement or not. There are two possible viewpoints in regard to this issue. The first may argue that repetition (by a different source) provides independent verification of the original task, thus providing a "*high degree of assurance.*" Such a viewpoint can argue that independent repetition in validation is almost required by
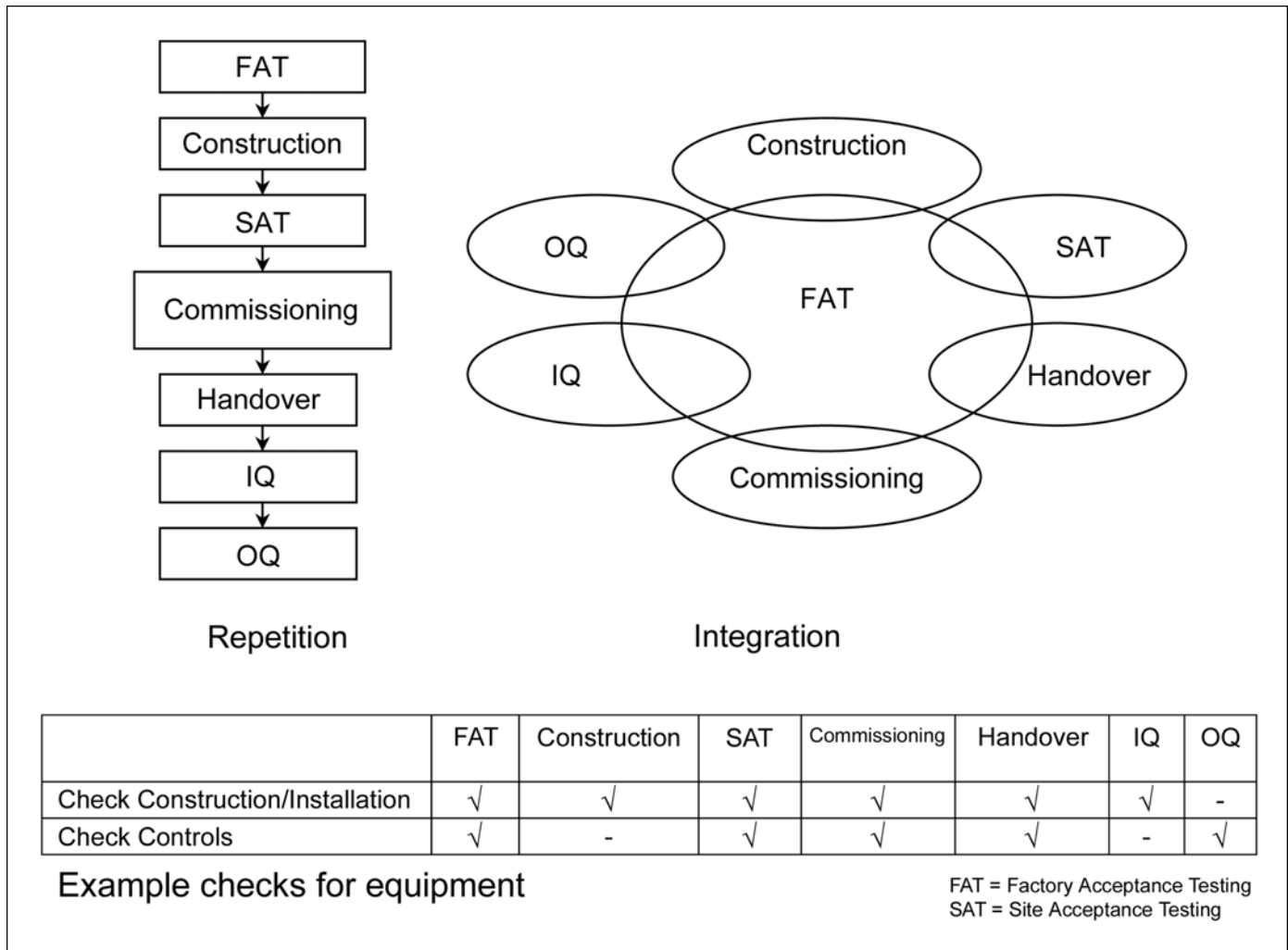
Figure 5. Duplication of tasks vs. information sharing.

definition. However, the other viewpoint can argue that if the task is performed correctly the first time, again with a "*high degree of assurance,*" then repetition will not add any value in terms of this degree of assurance. Indeed, what matters is that the procedure is performed correctly. If it is performed incorrectly, then no matter how many times it is repeated, that won't make it valid.

To clarify the latter viewpoint, take as an example a company procedure which states that an instrument is to be calibrated in a certain range. If the actual operating range of the process is not included in this calibration range, then no matter how many times this calibration is performed according to this procedure, it will be of limited value from a compliance stand point. On the other hand, if the procedure specifies the correct calibration range, and the actual calibration is done accordingly, then even if it's done just once (within the calibration period and without due cause for recalibration), then it should be in compliance. Furthermore, when a company calibrates its master instrument that it uses as a reference for the rest of the in-house instruments of the same type and range, it typically sends it to be calibrated in a nationally or internationally traceable calibration lab. After receiving the calibrated instrument, it doesn't send it

off to another traceable lab to have it recalibrated, why is this so? One can argue that it is because the "*degree of assurance*" is inherent in the procedure, rather than how many times it is performed. This clearly ties back to the issue of the levels of verification mentioned above.

It should be emphasized that these concepts apply to well defined and well understood tasks that can be unambiguously analyzed and tested. Such tasks are fairly simple conceptually, and are typically parts of IQ and OQ, where testing involves checking connections or testing switches, instruments, and controls, etc. However, other tasks have inherent variability and are not always completely understood, and may often involve an interplay of several factors. Such tasks are typically found in PQ, validating sterile facilities, and similar issues. In such cases, one can't ignore this complexity and several runs are required to understand the interactions let alone verify a property. For statistical significance, repetition will probably be way beyond even the famous three consecutive runs. Thus, the duplication we suggest eliminating is that related to qualification activities and not the actual validation of the process which typically takes place after qualification.

Having mentioned all that, we do acknowledge that the

issue is open to debate and interpretation, and perhaps even to a sense of security (thus subjectivity) that differs from one individual and company to another.

The Challenge

In summary, we believe the proposed approach will simplify and automate validation documentation, improve the validation process, and integrate it more effectively with the rest of the business process. This, in addition to the better definition of the scope of validation and the elimination of duplication of tasks, will reduce the time spent in validation and hence time to market. It is also expected to reduce the costs associated with validation both indirectly by reducing the time and manpower spent on it, and directly by improving the quality of the practice. At this point, one would be tempted to ask whether there are any problems associated with this approach. Naturally, there are several challenges involved.

A technical challenge to show that the information based approach described above, based on emerging ISO and XML standards, will actually improve the quality of information. And, that it can be implemented in an electronic environment that is both secure and usable. Also, like any other IT approach, it has to be validated. These are the areas that eValid is working on.

A cultural challenge also exists as is common with many major shifts in concept. Having solved the technical challenge, it has to be demonstrated that the migration to the new environment will not increase the risk to the patient, the business, or the regulatory process. Supporting evidence from similar (in regulatory terms) industries would be helpful. A more pronounced cultural challenge; however, is on the part of the pharmaceutical community - including suppliers and regulatory authorities - to adopt such a shift in paradigm.

Finally, there is an economic challenge to prove that applying such a methodology will actually lead to economic benefit. This is discussed in more detail below.

The Cost and Value of Validation

To investigate the value added by validation to the overall business process, we need to look at a more fundamental issue, and that is why do we perform validation. The obvious answer is that it is a regulatory requirement, but other than that there are several business incentives.

1. Due to limited sensitivity, some end product testing may not detect lower levels of non-conformance.

2. Some end product testing is destructive (e.g. sterility testing), thus should be reduced to a minimum but this would undermine its value.

3. Testing based on sampling can never provide a complete degree of assurance. This is the stance taken by the USP regarding sterility testing.

4. Validation is conceptually a QA function, and as such, provides the many benefits associated with QA such as lower reject, less waste, less rework, and less recall.

5. It also provides better understanding of the process, and hence, can serve as a basis for process optimization.

The above benefits, while making good engineering and business sense, are associated with most QA programs as applied in any other industry. It is clear that it is the regulatory requirement that makes validation so compelling. Indeed, if validation is not performed and the company fails an inspection, the consequences can be grave, even catastrophic. This indicates the importance of the cost of validation, more precisely the cost of not doing it rather than the cost of doing it.

One of the goals of eValid was to quantify the economic gains accrued by implementing its methodology. This has turned out to be more difficult than expected, as the costing of validation to begin with is not so straightforward to calculate. This may be due to the wide variability in the scope of validation between firms as mentioned earlier. In the case where validation is contracted out, the cost of validation for the owner is the amount paid to the contractor; however, still the costing performed by the contractor needs to be modelled and understood. As for the case where validation is done in house, the costing is even more difficult since some of the tasks may be performed as a part time activity by some employee, or as part of some other task. In addition, there are the costs associated with the delay in production, the material used in the validation tests, etc. The eValid team has decided to look more deeply into this issue, and has submitted a proposal in collaboration with the Manchester School of Management for a project to develop a cost model for validation. It should be noted that previous work has been published in Pharmaceutical Engineering for a cost model for non-conformance.[7]

The Time is Right

The essence of the eValid approach is to treat validation as an information management and information quality problem, thus allowing the use of technologies that are being applied to such problems in other industry sectors. If the methodology can reduce the volume of paperwork, many of the duplicate tasks will be eliminated. It is also likely that the analysis work of eValid will result in classification structures which have the potential to be associated with risk profiles. This will reduce the areas of personal interpretation, and increase areas of consensus on how much is enough. We believe that the approach developed and proposed by eValid is both relevant and timely. First, because there is consensus in the industry that there are problems in the way validation is currently performed and there is potential for improvement. The publication of such guides as the ISPE Commissioning and Qualification Guide and GAMP 4 indicates the presence of the problems that those guides address. Second, the utilization of an information based approach is inline with the recent regulatory trend toward encouraging electronic submission, and enforcing requirements concerning electronic records and signatures, 21 CFR Part 11. Third, there is a regulatory trend toward utilizing the concepts of risk man-

agement and in general putting more structure, and thus, predictability in the inspection process. Last but not least, is the economic factor. The recent or expected expiration of patents of many blockbuster drugs, and the lack of development of financially equivalent replacements have put economic pressure on pharmaceutical companies. Thus, an approach that reduces time to market would be welcome. In addition, companies may consider cutting costs in areas where they traditionally might not have considered, such as validation, manufacturing, or other activities downstream R&D. We believe that the approach proposed will meet the needs and trends mentioned above, and is thus very timely.

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About the Authors

Hosam Aleem is a Research Associate in the Manchester Centre for Civil and Construction Engineering at UMIST. He has an MS from the University of Missouri – Rolla and an engineering degree from the University of Southern California, both in electrical engineering. He is currently studying for an MSc in Biotechnology at UMIST. His industrial experience includes several years as an instrumentation and process control engineer in the oil and gas industry, and as a validation and calibration engineer in the pharmaceutical industry.

Manchester Centre for Civil and Construction Engineering, UMIST, PO Box 88, Manchester M60 1QD, United Kingdom, email: h.aleem@umist.ac.uk, tel: +44-161-200-8966.

Stuart Lord is a Mechanical Engineer by trade, and has spent his career in the process industries. He has spent many years in IT, where he has had responsibilities for developing and supporting CAE and business systems as well as managing user support and IT infrastructure. Most recently, he has managed collaborative projects, particularly those associated with the development of standards that define the

meaning of information. For the last few years, he has been researching information management in validation, managing a research project at UMIST, and running his consultancy business.

Servblock Ltd., Nevada Tempest Rd., Alderley Edge, Cheshire SK9 7BU, United Kingdom, email: s.lord@umist.ac.uk, tel: +44-161-200-8966.

Tim McCarthy is a Senior Lecturer at UMIST, which he joined in 1985. Prior to this, he worked as a Research Engineer in the Hydraulics and Maritime Research Laboratory at the University College Cork where he earned his PhD. He also has spent time working with Ove Arup and Partners in their Cork and Paris offices. In 1994/95, McCarthy worked at Stanford University's Blume Center for Earthquake Engineering and Center for Integrated Facilities Engineering. He holds degrees from UCC, Cranfield University, and is a member of the Institution of Engineers of Ireland. His current research interests include knowledge management and information management in regulated environments.

Manchester Centre for Civil and Construction Engineering, UMIST, PO Box 88, Manchester M60 1QD, United Kingdom, email: tim.mccarthy@umist.ac.uk, tel: +44-161-200-4609.

Paul Sharratt joined the department of Chemical Engineering in 1991. Prior to that, he was a process engineer at ICI (now part of Syngenta). He has been awarded a Royal Academy of Engineering /EPSRC chair in Innovative Manufacturing for five years starting in 2001. His research interests are in process design, environmental management, and reaction engineering. He has primarily focused on fine/effect chemicals processing and manufacturing strategies (the BRITEST project) and low tonnage chemical processes.

Department of Chemical Engineering, UMIST, PO Box 88, Manchester M60 1QD, United Kingdom, email: paul.sharratt@umist.ac.uk, tel: +44-161-200-4367.

Yuyang Zhao is currently a Research Associate at UMIST working on the eValid Project. He holds a PhD in chemical engineering from Dalian University of Technology, China. His experience is in the area of operation and management computer modelling for oil and gas, chemical, and the pharmaceutical industry.

Manchester Centre for Civil and Construction Engineering, UMIST, PO Box 88, Manchester M60 1QD, United Kingdom, email: y.zhao@umist.ac.uk, tel: +44-161-200-8966.

From Never to Forever: Document Retention Policy

by Mark Kropp, MD

This article supports the writing of a document retention policy and gives general time retention periods for different kinds of documents including electronic copies. It outlines planning for retention and can be used when programming current compliance software packages.

Introduction

Document retention is a significant technical challenge for the pharmaceutical industry as well as all businesses. Many of the Knowledge Management Engineering Software Packages sold as compliance tools require decisions regarding document retention. Because of the importance of the issue to pharmaceuticals and customers, as well as the potential for disputes or litigation, document retention is a "business necessity." It involves both company internal systems as well as projects that the company has undertaken on behalf of clients. However, the purpose is not to retain every piece of paper or electronic information ever created during the course of a project, but to retain the documentation which allow the company to respond to customer, client, and government inquiries, or to show what the company did on a particular project and that the company complied with its obligations.

Competitive pressures, government regulations like Health/Insurance Portability and Accountability Act (HIPPA), Gramm-Leach-Bliley, 21 Code of Federal Regulations (CFR) Part 11, and recent media coverage of sensitive corporate e-mail being exposed, are all driving organizations to focus on secure electronic documentation. One of the many lessons learned from the "Anderson trial," with its focus on document shredding and the prevalence of such electronic evidence as emails, is not just the potentially incriminating nature of electronic archives, but the liability of inadequate enforcement of a document retention policy. It's one thing to have a policy; it's another to implement and audit it.

On July 30, 2002, the President signed into law the Sarbanes-Oxley Act of 2002. Enacted in response to the recently exposed corporate and accounting wrongdoing, the "Act" contains some of the most significant changes to the federal securities laws since their enactment during the Depression. The "Act" creates a new federal accounting oversight body; revamps auditor independence rules; enacts new corporate responsibility and governance measures; enhances disclosures by public companies; regulates potential conflicts of interest by securities analysts; strengthens the powers and resources of the Securities and Exchange Commission, and imposes new penalties for securities fraud and related wrongful conduct.

Information Protection

An effective information protection program cannot be solely defined in terms of trust. Rather, it must be based upon the same prudent business practices that applied to earlier manual systems and statement/publication of policy, careful definition of individual responsibilities, separation of controls, maintenance of audit trails, protection of vital records, and access to limited information, based on "need to know." These are all controls, and are exactly what auditors look for.

Table A. Document retention decision tree.

	Yes	No
Is there a legal requirement to retain the document?	Yes	No
Is there a use for the document after its intended use?	Yes	No
Is there a consequence for not being able to locate the document?	Yes	No
Can the document be reproduced?	Yes	No
Can the document be retained?	Yes	No
Is the document important for pending or threatened litigation?	Yes	No

Document Retention Policy

Some of the positives that can begin to result from publishing document retention policies/guidelines are:

- greatly improved document retention focus
- fewer litigation incidents
- fewer audit concerns/comments
- greatly improved business focus
- enhancement of the professional perception of the business
- fostering of a team oriented environment
- enhancement of employee morale
- helpful in attracting and retaining the best people

Some objectives are:

- control who can see information and whether they can print, copy, or select text
- prevent information from being forwarded
- recall or expire information, even after it's accessed
- track what recipients do with your information after they download it

Responsibilities and Policy

The Sarbanes-Oxley Act of 2002 requires enforced records management programs at US companies and shifts personal accountability to executives:

Title VIII: Corporate and Criminal Fraud Accountability Act of 2002.

It is a felony to "knowingly" destroy or create documents to "impede, obstruct, or influence" any existing or contemplated federal investigation. Auditors are required to maintain "all audit or review work papers" for five years. The statute of limitations on securities fraud claims is extended to the earlier of five years from the fraud, or two years after the fraud was discovered, from three years and one year, respectively. Employees of issuers and accounting firms are extended "whistleblower protection" that would prohibit the employer from taking certain actions against employees who lawfully disclose private employer information to, among others, parties in a judicial proceeding involving a fraud claim. Whistle blowers are also granted a remedy of special damages and attorney's fees. A new crime for securities fraud that has penalties of fines up to 10 years imprisonment.

Companies, in anticipation of potential litigation, should have a document retention policy set up, and they need to operate within a policy created by their lawyers and to enforce it regularly so that they can be certain they are operating within the realm of the law and protecting themselves from potential harm.

Not having a policy, or having one, but not acting on it on a regular basis is a problem, as was illustrated by the "Anderson trial." If a document retention policy is acted on only before pending litigation, a company's actions may not hold up in court.

Preventative maintenance, including the education and training of employees on the policy, is essential to ensure the policy is enforced. Management and counsel should work together to test the effectiveness of the policy by conducting periodic searches of the data environment to see whether or not anything of interest turns up. If something is found, counsel and the client discuss the ramifications and develop a strategy for dealing with that data or problematic behavior before anything gets to the point of litigation so that the firm is protected and doesn't incriminate itself by keeping needless files that it has a right to eliminate.

Destroying incriminating evidence or unethical behavior isn't implied here, rather data that isn't official communication, such as working drafts, and day to day email with no future value, certainly, if there is anything that could be perceived as a "smoking gun," it is better to know about it, to minimize litigation risks. It's critical that companies know the contents and mange their information archives. Doing so forces employees to prioritize, to conserve network storage, and to conduct themselves ethically.

If a policy exists, it needs to be audited. If one says these are things done and aren't, how does one know employees are following the policy? Does one want to put Information Technology (IT) departments in the difficult position of auditing and scrutinizing the integrity of co-workers? One needs to periodically pull in a third party firm to audit adherence to "communication" policy. Recent events and trends suggest that as firms become involved with lawsuits, business leaders begin to appreciate the value of managing the risk. Insurance rates are going up, and eventually companies are required to enforce and audit their document retention policies with third party risk management firms in conjunction with attorneys.

Although this is a cost containment and risk management expenditure for corporations, businesses need to understand it is a critical one, because the costs of not developing, enforcing, and auditing a document retention policy could be devastating.

A document retention policy is a set of guidelines that a company follows to determine how long it should keep records, including email, web pages, quality documents. The policy is important for many reasons, including legal requirements that apply to some documents. Why and how long is the next question. Occasionally clearing away unused items is necessary; however, tossing the wrong paper or deleting a critical data file can have dire consequences, especially for pharmaceuticals.

Document retention policies can range from a few paragraphs to many pages. A good document retention policy answers the question: "What can I throw away (delete), and when?" Some policies contain detailed instructions for where documents will be kept, the type of storage container, and the manner of disposal (such as shredding). Most policies provide a list of the types of documents produced and how long those documents should be kept. For example, our Clinical Research Organization (CRO) contracts five year retention with subsequent returning of all documents to the client.

Today, a good pharmaceutical document retention policy deals with electronic files and electronic mail. The objective of a document retention policy is to reduce the volume of paper in storage, or data on disk, meet legal requirements for record keeping, and stem paranoia.

Six Issues for Consideration

How long to keep a document, when and how to store the document, and how to dispose of the document will depend on the type of document – *Table A*. Six issues for consideration are:

1. Is there a legal requirement for keeping the document? Legal requirements include federal, state, and local reporting concerning various regulated matters, such as wages and hours, health and safety, shipment and handling of hazardous materials, quality and engineering documents.

2. After the item is used for its intended purpose, what other purpose could it serve? Can it be used to support or oppose a position in an investigation or litigation? Can it support tax deductions? Is it used in application for Food and Drug Administration (FDA) approval?

3. What is the consequence of not being able to locate the document? If the document was destroyed pursuant to a records-retention program and no threat of litigation was pending at the time, the issue will be how reasonable the program was. If the item was mentioned in a lawsuit, then suddenly destroyed, the presumption will be that the destruction was accomplished deliberately.

4. Can the item be reliably reproduced elsewhere if needed? Is the information available from the public library, an online source, a database, or company central file? For example, our CRO sends the same memorandum to multiple recipients and each does not keep a copy.

5. Once the possible use of a particular item is determined, the question becomes how long to retain the document. This question is answered by reviewing the statute of limitations (the time within which a suit must be brought for a particular action after the action is discovered) in both state and federal government regulations.

6. If the document is in any way related to pending or threatened litigation, it is wise to keep the item until the matter is finally settled or all appeals are exhausted.

The following examples are drawn from the web. The recommended retention period exceeds the required statute because the limitations period for litigation is longer than the statutory record-keeping requirement.

Email and Web Pages

The length of time email should be retained depends on the content. After an email is forwarded with the "latest joke" to all, it can probably be deleted (unless it's one of those kind of jokes, at which point it will likely be attached to a complaint for harassment). It is suggested that a hard copy of important email be kept in the file to which it pertains. It is a good idea to have backup documentation, especially if a system may fail (crash). Some systems are archived immediately, overnight, on weekends. While this may preserve a snap shot of the system, most backups are lost when the same media is used for the next backup. In other words, don't rely on the fact of a backup to preserve important email. It is a good idea to preserve each iteration of a web page, especially if a dispute arises.

Employee Records and Employment/ Training Manuals

Employee records should be retained for the length of the employee's tenure with the company, plus at least the statute of limitations period. Many policies require records to be kept for at least seven years. Payroll records should be stored for the same period as tax records. Most state laws require that any action by an employee based on discrimination must first be filed with the Equal Employment Opportunity Commission or the state equivalent within 180-300 days of the act giving rise to the complaint. A formal lawsuit in state or federal court may be filed after the administrative agency has completed its review or within six months of the administrative filing. Most states allow these types of suits to be filed within two years of the act, giving rise to the complaint. Other causes of action, such as breach of contract or various tort actions (such as infliction of emotional distress or wrongful discharge) have limitation periods varying from one to six years. Suits can last for many years, and the documents must be preserved throughout the suit. Because employment records can contain very sensitive information, they should be stored in a secure area. Certain types of records, such as the Immigration and Naturalization Services I-9 form should actually be kept separately from active employee files to avoid claims of national origin discrimination. When these documents are ready for destruction, they should be shredded to avoid disclosure. A copy of each version of employment and training manuals should be kept with the dates that version was in use. The reason for, or timing of, a change in the manual may become important in a suit.

Sales Documents Including Records and Presentation Materials

The recommended retention is the length of the sale plus the limitation period. Many policies require that such records be retained for anywhere from three to seven years. The records should be kept, unless the information can be reproduced elsewhere, for as long as needed to protect the company in the event of legal action. Correspondence leading up to a sale, as well as the sales materials that resulted in the sale, may serve as evidence of promises made to make the sale. Solicitation letters for products or services not purchased need not be retained. Like employment manuals, a copy of each ver-

sion of sales document should be kept with the date that version was in use. Some companies keep market research and projections for as long as 20 years, as they serve the purpose of historical comparison. This points up the need to evaluate the type of document and determine how to treat it.

Tax Related Documents

The recommended retention is seven years. If tax audits go back three years from the date the return is filed, and six years from that date if fraud is suspected, taxes are filed each year after the tax was incurred so keeping the supporting documents for seven years should cover audits.

Real Estate Records

The recommendation is to check with an attorney in the state of the holding, but on average, 20 years because the statute of limitations for real estate is long in most states and often to prevent squatters from claiming possession of land by reason of having lived on the land for an uninterrupted period of time this time is needed. This means the actions concerning real estate can be brought in some cases up to 20 years after the action arose.

21 CFR Part 11

Subpart B - Electronic Records

<u>11.10 Controls for closed system</u>

c. Protection of records to enable their accurate and ready retrieval throughout the records retention period. (Goes to predicate rules).

Medical Devices

Goes to product liability and government regulation. The saying is "one year from forever;" however, the life of the product is also a timeline often used.

Inventions

The recommended retention is permanently. An intellectual property registration (patent, trademark, copyright) can always be challenged. Documentation relating to the date the invention was conceived, the trademark first used, or the copyrighted item first published, can be vital.

Summary

A. Recognize that implementing a document retention policy has a legitimate purpose. If there is no business reason to keep a document and no legal obligation to retain it, it can be destroyed, as a matter of practice, in order to reduce storage costs.

B. Ask an attorney to write the policy to assure the criteria chosen (usually based on the date the document was created) are legally correct. The purpose of the policy is not to evade the law or to create a legal problem. The purpose of a legitimate document retention policy is to manage, properly and legally, the mass of documents that a corporation generates.

C. There is no wisdom in "aggressive" or "clever" legal positions when adopting and implementing a document retention policy. Current events demonstrate the price of the folly and that paid by those who do.

D. Do not destroy documents if a legal "matter" is pending. Clearly, a court proceeding is a "matter." A grand jury investigation is a "matter."

E. Do not distribute a document retention policy without explanation as how to apply it. Any document retention policy should be accompanied by written guidelines on how to apply it along with periodic training on its proper use.

F. Do not implement a document retention policy in haste at a time of crisis. This will become the worst time and approach. Also, worse then a bad document is an illegally destroyed document.

G. Teach how to properly prepare internal documents. Retain those data required by law. Finally, do not let the law be misstated or allow any erroneous jumping to legal conclusions.

About the Author

Mark Kropp, MD is Manager of Computer Validation at In Vitro Technologies, Inc. based in Baltimore, Maryland. He has more than 15 years of validation experience including working with Bayer, Alza, and Johnson and Johnson. He can be reached at (410) 455-1242.

In Vitro Technologies, Inc., 1450 S. Rolling Rd., Baltimore, MD 21227.

This article describes how to adopt a risk-based approach to 21 CFR Part 11 (Part 11) assessments for computer systems used for cGMP relevant activities within the pharmaceutical industry.

Adopting a Risk - Based Approach to 21 CFR Part 11 Assessments

by Ken Phoenix and John Andrews

Background

In March 1997, the FDA issued final regulations to 21 CFR Part 11 (Part 11) that provided criteria for acceptance by the FDA, under certain circumstances, of electronic records, electronic signatures, and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures executed on paper. These regulations, which apply to all FDA program areas, were intended to permit the widest possible use of electronic technology, consistent with the FDA's responsibility to protect the public health.

The final regulations became effective in August 1997, and since that time, they have been the subject of ongoing debate within the pharmaceutical industry on interpreting how and when the regulation should be applied. Industry concerns center around:

- restriction of technological innovation
- lack of clarity on how the regulation should be applied for specific applications
- significant cost increases for implementing computer systems within the cGMP-relevant environment

The topics for debate centered on the Part 11 requirements for validation, audit trails, record retention, record copying, and legacy systems, and the situation was made worse by comments from the Agency's staff being misinterpreted as FDA Policy.

There also was significant 'interpretation' and individual assessments that muddied the waters further – it was never intended that it should restrict technological innovation nor add a significant cost burden on the computer system validation and cGMP compliance activities.

For the industry, the introduction of Part 11

heralded a significant growth in the Computer validation work, and some members of staff now have primary responsibility for Part 11 and are industry-recognized experts in the field. Don't undervalue them, your trained resources still have an important job to do in helping you remain in compliance with Part 11.

The cost of achieving a degree of independence from external expertise has been significant for many pharmaceutical companies, and today, they have the opportunity to reap the benefits that Part 11 compliance can bring, including:

- start to realize the vision of 'going paperless'
- added security
- knowing who was at the controls during any stage of production
- having the audit trail, electronic records and signature capabilities required by regulation
- reduction of costs by eliminating unnecessary paperwork
- quicker NDA submissions and faster time to market
- higher degree of quality and consistency – reduced human error
- ability to view data in context with automatic management and incident report generation
- smoother regulatory inspections

A New Direction: A Risk-Based Approach and Smart Regulations

Faced with industry concerns and an ever-growing burden of undertaking regulatory inspections, the FDA announced a highly significant change of direction in August last year to improve regulation within pharmaceutical manufacturing.

The FDA's Health and Human Services (HHS) Secretary; Tommy G. Thompson has set

out to introduce sweeping reforms in the HHS regulation with the stated goal of introducing smart regulations to improve access to quality healthcare and services.

Mark B. McClellan, MD, Commissioner of Food and Drugs underpins this "These initiatives are Part of the Department of Health and Human Services' overall efforts to improve the quality, safety, and cost of medical products."

The initiative "Pharmaceutical current Good Manufacturing Practices (cGMPs) for the 21st Century: A Risk Based Approach," is a two-year program which applies to pharmaceuticals, including biological human drugs and veterinary drugs.

Mark McClellan's statement, "We will focus our attention and resources on the areas of greatest risk with the goal of encouraging innovation that maximizes public health protection and promotion," portrays the essence of the change.

Consequently, in a move that surprised much of the pharmaceutical industry, the *Federal Register* of February 4, 2003, announced the withdrawal of the draft guidance for industry, *21 CFR Part 11; Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records.*

Since this announcement, confusion has been expressed and strenuous efforts by the FDA to clarify their intent has resulted in yet more confusion.

Most importantly, the FDA has not withdrawn Part 11 and records must still be maintained or submitted in accordance with the underlying predicate rules.[1]

There are significant implications in the detail, but the broad aims of the FDA when they withdrew the Part 11 Guidance are simple enough to understand:

- to facilitate innovation for modern manufacturing, electronic record keeping, and regulatory submissions, and allow manufacturers to make certain types of changes in their processes without prior FDA approval

- to exercise enforcement discretion with respect to certain Part 11 requirements while FDA considers whether to revise the Part 11 regulations

- The FDA will not normally take regulatory action to enforce Part 11 with regard to systems that were operational before August 20, 1997 while FDA considers whether to revise the Part 11 regulations.

- Part 11 will be interpreted narrowly, and subject to FDA clarification, fewer records will be considered subject to Part 11.

The new draft, "Guidance for Industry Part 11, Electronic Records; Electronic Signatures - Scope and Application," issued in February this year is currently available for industry comment. This Guide replaces all other Part 11 guidance and the FDA's Part 11 enforcement policy.

This draft guidance attempts to define:

- Narrow Interpretation of Scope - stating that the *merely incidental* use of computers would not trigger Part 11

- Definition of Part 11 Records - recommending that, for each record required to be maintained by the predicate rules, you determine in advance whether you plan to rely on the electronic record or paper record to perform regulated activities and document your decision. Business practices also may be taken into account to determine if Part 11 applies.

- Validation - should be based on the predicate rules *and* ensuring the reliability and accuracy of the Part 11 records. The FDA recommend that you base your approach on a justified and documented risk assessment to determine if the system will affect product quality and safety and record integrity

- Audit Trail - where the FDA plans to exercise 'enforcement discretion' regarding the specific Part 11 requirements for computer-generated, time-stamped audit trails. Again, a documented risk assessment is recommended when considering the design of the audit trail.

- Legacy Systems - where the FDA plans to exercise 'enforcement discretion' regarding the specific Part 11 requirements with regard to systems that were operational before August 20, 1997. However, all systems must comply with all applicable predicate rule requirements and should be fit for their intended use.

- Copies of Records - that defines the requirements for creation, copying, and review of the records

- Record Retention - where again 'enforcement discretion' is intended. A documented risk assessment also is recommended when considering the design of the system for protecting the records throughout the retention period.

There is much in the new draft guideline that requires questioning (and has been), and key terms such as 'enforcement discretion,' unfortunately, remain undefined.

However, what is significant is the repeated reference to a 'documented risk assessment' in the recommendations, but how should this be done?

Example of a Risk-Based Approach to Part 11 - Building Management System

The control systems associated with building environmental management, typically known as Building Management Systems (BMS), have always presented a difficult challenge to those responsible for validation. This is because cGMP and non-critical facilities are generally housed in the same building. Therefore, the control systems have generally been mixed, thus making it very difficult and expensive to validate. Segregating the control system between cGMP and non-critical also is very difficult because the air-handling equipment and other such equipment may be common to both facilities. They are often considered to be too difficult to validate, but the regulators are unconvinced. A typical FDA

Warning Letter illustrates the point:

> *The alarm system that communicates, records, and controls alarms such as air balance and temperatures for production, warehouse and testing areas lacked validation documentation (FDA Warning Letter, January 2001).*

A typical Building Management System is shown in Figure 1.

The system unifies the environmental and security data from the manufacturing plant, cleanrooms, gowning rooms, physical points of access, etc., for presentation to the plant managers and operators. Electronic records are generated and stored on a secure server for future regulatory review.

Specific areas of importance from a Part 11 viewpoint include:

Security - *Physical and Logical*

- Typically, the standard 'two-token' username and password combination are used within a Part 11 compliant environment for logging onto the BMS computer systems.

- Physical security of access to the facility may be provided by swipe cards, proximity cards, biometrics, and video surveillance, or a combination of these.

- The requirements for adequate physical security are specified in 21 CFR Part 11.10 that defines the measures to ensure the authenticity and authority level of personnel with access to restricted areas and workstations.

- The system is configured to generate an alarm if an attempt is made to gain unauthorized access or initiate a lockout if there are multiple failed access attempts. This can then be recorded in a report for the inquiry team.

- The movement of personnel and computer log-on/log-off must be recorded and reproduced using electronic records. Furthermore, access restrictions can be introduced in specific zones of the plant.

- Within the computer systems log-on security can be tiered, e.g., operator, supervisor, manager, engineer, such that
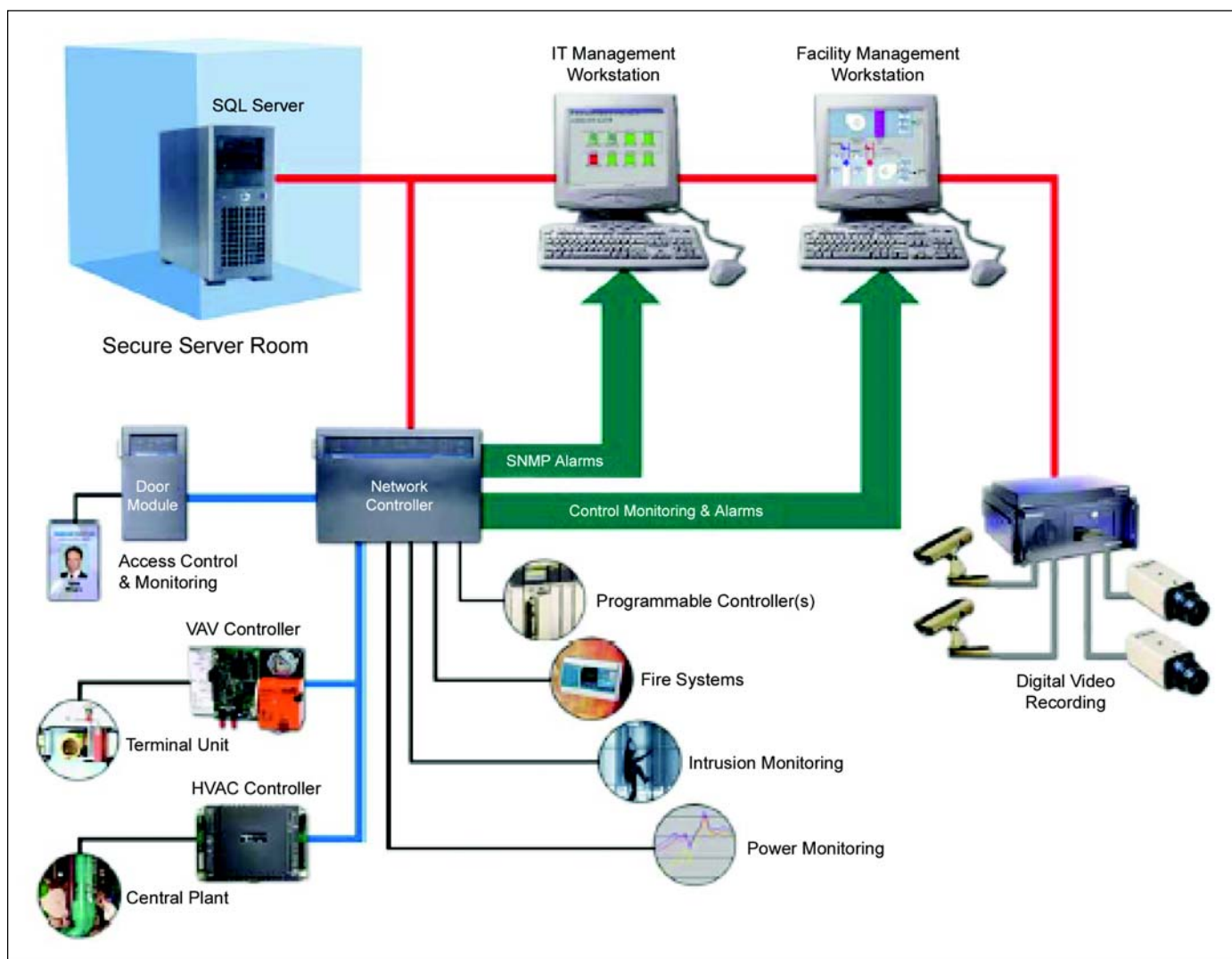

Figure 1. A typical building management system. (Image courtesy of Andover Controls Europe.)

individuals have pre-defined access rights to the system functionality.

• Part 11 extends to protecting the environment in which the records are stored, e.g., secure server and archive room.

Environmental Controls

• Controlling the nature and quality of air in a manufacturing facility can be of paramount importance and deviations can dramatically adversely affect the end product quality.

• The 'Environmental Control' aspect of the BMS system is therefore a cGMP-critical attribute of the overall system.

• The control systems can be very complex, going far beyond the simple temperature and humidity control provided by simple HVAC systems.

• The controlled parameters could be temperature, humidity, particulate counts, differential pressure, lighting, gas levels, etc. This extends to the laboratory where additional equipment may be required to detect toxic gases and fume hood positions.

The BMS-controlled and monitored parameters are recorded electronically to provide the operational staff with a view of current conditions and provide evidence of the overall quality and safety history of the facility.

The data from the BMS system can be analyzed and correlated, e.g., a temperature alarm can be traced to an individual entering part of the facility and holding the door open, and the alarm and event reports can be compiled to convey meaningful information.

For a BMS system, the following topics might be included in the risk assessment:

• uniqueness of username/password token
• access rights for different employee types
• means of obtaining physical access - swipe card, biometrics, etc.
• audit trail for electronic records
• security of access for records
• server security
• data archiving and retrieval - media type and storage conditions
• user log -on and log -off audit trail
• authorization to cancel alarms and warnings
• periodic review

The above gives just a few examples; a definitive list would need to be compiled for each application.

Executing the Risk Assessment

The principles of risk assessments can be summarized as follows:

1. Identify the potential risks.

2. Assign the inherent severity (worst case impact) and probability (assessment of the likelihood of the event happening) associated with each risk, e.g., high, medium, and low severity; high or low probability.

3. Identify measures that can be taken to reduce the impact of high/medium severity and/or high/medium probability risks. (The objective is to design measures that, ideally, reduce both the probability and severity to 'low – low').

4. Assign the expected residual severity and probability to each identified risk *after* the corrective measures have been introduced.

For example, a data server may be currently located in an open office - the *inherent* probability of someone tampering with it is high and (as it contains cGMP-critical data) the severity (impact) of unauthorized access also will be high. This is a high-risk installation for Part 11 compliance.

The control *measure* would be to re-locate the server in a secure room with restricted access.

The *residual* probability and severity of the risk should then be 'low-low' assuming that the new location has been correctly designed and it is used as intended.

While the risk assessment process is simple in principle, the reality of executing it can be more complex.

For example, the desired control measure may not be capable of implementation for practical reasons or cost constraints - alternative approaches will then have to be devised, e.g., additional procedural controls administered by the companies quality assurance functions.

Another situation that arises is the introduction of *secondary risks* that are introduced as a consequence of introducing a control measure. Using the simple example above, re-location of the server may have removed it from an area where Uninterruptible Power Supply (UPS) support was provided and an additional UPS may have to be purchased to remove the secondary risk.

There are a number of standard risk assessment techniques available and the Failure Mode Effects Analysis (FMEA) approach, for example, is widely used within the industry. The following approach has been developed specifically for the data management requirements of 21 CFR Part 11 where the probability of the risk arising and the probability of detecting the error are the risk assessment parameters.

After completing the following three steps, the records deemed high/medium risk from the results of the risk assessment should then be further assessed against audit trails and record retention requirements of relevant predicate rules. Using this assessment tool looks easy, but will highlight the gaps in normal operational expectations to comply with the narrowed interpretation of Part 11.

Step 1 - Does the System Impact Part 11?

Does the system manage, store, or use GxP electronic records? Y/N

Consider:
Are the records required by predicate rules and maintained in electronic format? Also, are the records required by predicate rules maintained in electronic format and paper format where the electronic format is relied on to perform regulated activity?
Note: Review business practices to ensure the electronic format of a record is or is not performing a regulated activity. Is this document in an SOP?

Does the system impact Predicate Rule requirements? Y/N
Consider:
Was the system in place before August 20, 1997? If the answer to the question is Yes, Part 11 may not apply. Review current use against predicate rule requirements. If the answer to the above question is Yes, has there been any major upgrades made to the system since August 20, 1997? If Yes, Part 11 may apply.
Note: Are records in electronic format in place of paper format, if Yes, Part 11 would apply?
Or: Is the system used to generate paper print outs of electronic records, and those records meet the requirements of the predicate rules, and persons rely on the paper to perform regulated activities; if Yes, Part 11 would not apply? Is this document in an SOP? Also, what happens to the electronic record?

Is the system used to approve and/or authorize GxP operations, or to authenticate GxP electronic records by means of an electronic signature or other electronic mechanism? Y/N
Note: Paper and e-records and signature components can co-exist as long as predicate rule requirements are met and the content and meaning of the records is preserved.

If the answer to the above three questions is No, then Part 11 does not apply.

Step 2 - *Risk Management*
Produce a process flow diagram identifying all major functions, interdependencies, i.e., network connections, other computer systems, and peripherals like printers, interfaces with people including the SOPs.

- *What are the major GxP functions and associated performance requirements of the system?* - list all the major systems functions and any performance criteria; this information can be derived from the flow diagram and the User Requirement Specification/Functional Specification for the given system.

- *From the major functions, what GxP data is produced and how does it impact predicate rule requirements* - this information can be derived from the systems design documents.

- *If the system fails to perform a function that impacts on predicate rule requirements correctly, what are the failure events?* - from the list of major functions, look at the different types of failures that may exist in the operating environment.

- *What is the effect on GxP of each failure event?* - assess if there is an impact GxP for each failure event.

- *What is the probability of each failure effect being detected?* - categorize into low, medium, or high probability of detection in a normal production environment.

Major functions?	What GxP data is produced?	Failure events - identify the risks	What is the effect on GxP of each failure event?	Impact on GxP (Y/N)		Probability of Detection?		
				Y	N	L	M	H
Patient history file	Baseline data recording patient 1st visit and history information	Incorrect baseline data recorded	Incorrect dose set	✓		✓		
			Incorrect study result	✓		✓		
		Baseline data lost	Study delayed		✓			✓
			Patient removed from study	✓				✓
	Study data results of all subsequent visit and test results	Incorrect study data recorded	Study results wrong	✓		✓		
			Study abandoned		✓	✓		
		Study data lost	Study delayed		✓		✓	
			Study abandoned		✓		✓	
	Visit data lists the number and dates of all planned visits and tests	Incorrect visits scheduled	Study results wrong	✓			✓	
		Visit history missing	Patient removed from study	✓			✓	
Note - above example for illustration purposes only								

Table A. Risk Assessment - example using an eCRF application.

Probability of Detection			
	High	Medium	Low
Probability of it Happening — High	Medium Priority	High Priority	High Priority
Medium	Low Priority	Medium Priority	High Priority
Low	Low Priority	Low Priority	Medium Priority

Table B. Risk prioritization.

- *Assess the probability of each failure effect happening* - categorize into low, medium, or high probability of it happening.

- *What modifications to the design or enhancements to SOPs can be made to reduce GxP risks* – Review findings and modify design to eliminate the high risk/high probability of it happening functions. Enhance SOPs to cover lower priorities. Use a Part 11 checklist to assess system compliance and likely resolution requirements - *Table A.*

In Table B, the baseline data and the study data are considered to be high priority if there is a medium to high probability of it happening and a medium to high priority if there was a low probability of it happening. Therefore, it is important to assess the full compliance status of this system and address any compliance deficiencies in relation to handling baseline data and the study data.

Having established the priorities, work can commence on designing the necessary corrective measures. When this is done, the risk assessment can then be re-executed to determine the residual risk - this is an iterative process where secondary risks may be identified along the way. When the risk assessment team is satisfied that they can achieve a 'minimum risk' solution, the Risk Assessment Report can be compiled.

Step 3 - *Part 11 Assessment*
Conduct a 21 CFR Part 11 assessment of the system using a standard checklist, e.g., using the ISPE GAMP Guide, to assess the likely remediation requirements to meet full compliance.

The structure of the Risk Assessment Report should clearly document the process you followed and it helps if you include the Part 11 requirements together with the questions you need to consider, as shown in Table C.

Conclusions
Following the principles described above should help guide the reader through a logical risk assessment, and hence risk management approach to compliance with 21 CFR Part11 in the context of the new direction being adopted by the FDA. The proposed changes to Part 11 are still in the draft/consultation phase, but the future direction the FDA wants to follow is already clear.

A clear, logical, approach to managing Part 11 compliance that has been correctly documented and followed through will help avoid difficult questions during your next inspection.

References
1. The underlying requirements set forth in The Federal Food, Drug, and Cosmetic Act (the Act) Public Health Service Act (the PHS Act) and FDA regulations are referred to as the *predicate rules.*

2. *Regulation: 21 CFR Part 11; Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records.* - FDA.

3. "Pharmaceutical current Good Manufacturing Practices (cGMPs) for the 21st Century: A Risk Based Approach" - FDA.

4. Draft: "Guidance for Industry Part 11, Electronic Records; Electronic Signatures - Scope and Application" - FDA, (issued Feb. 2003 with 60 day review period).

5. White Paper: "Smart Facility Automation Solutions For Regulatory Compliance" Andover Controls (www.andovercontrols.com).

Section	Preamble ref.	Questions to Consider	Part 11 Guideline comment
11.10(b)	69, 70	**11.10 (b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.** • Can a copy of a single record (in electronic format) be supplied to an inspector? In paper format? • Can a copy of the entire database (in electronic format) be supplied to an inspector? • Are procedures in place to describe HOW to accomplish these inspection tasks? • Are procedures in place to define what format the electronic records will be provided?	**You should provide the inspector with reasonable and useful access to records during an inspection** **Provide copies in common format where records are kept in these formats** **Or - using established automated conversion methods to make copies into a more common format** **If you sort, trend etc.; copies to the agency should also have the same capability** **Consider procedures and techniques to access records**

Table C. Risk Assessment Report.

6. GAMP 4, GAMP Guide for Validation of Automated Systems, ISPE (Publishers), 2001.

About the Authors

Ken Phoenix, **B.Sc.,** recently joined GxP from KMI-PAREXEL where he worked in Sweden on CSV projects for a major pharmaceutical/biotech company. Phoenix is now the Computer System Validation Group Manager for GxP. With a background in large process control and IT projects, he has been working exclusively on computer system validation projects for the past three years. He was born in Birmingham and has 16 years of experience in the pharmaceutical/biotech industry gained within Europe.

John Andrews is a Principal Consultant at the Synapse Partnership Ltd., Manchester, UK, and a member of the GAMP 4 Special Interest Group on Process Control. He also sat on the Editorial Board for GAMP 4. His responsibilities include providing consultancy on computer systems validation, compliance, and quality assurance activities within the pharmaceutical, biopharmaceutical, medical device, and other regulated healthcare industries. Previously, he was manager of IT Consulting Service at KMI, a division of PAREXREL International LLC, and held positions as computer system validation manager and supply chain systems project manager with GlaxoSmithKline. Responsibilities at GlaxoSmithKline included: all aspects of computer systems validation, from process control through to business and laboratory system validation. He managed the teams with responsibility for ensuring all computer system validation activities undertaken on site and within projects were to an appropriate level to comply with the regulator's requirements. Previous employment includes 15 years with SmithKline Beecham Pharmaceuticals where he held positions as a senior engineering standards engineer, secondary manufacturing electrical engineer, projects engineer, and electrical supervisor.

The Synapse Partnership Ltd., 207A Ashley Rd., Hale, Cheshire, WA15 9SQ United Kingdom, E-mail: john.andrews@synapse-partnership.com.

This article presents a process and operational documentation model for a typical biopharmaceutical manufacturing system. Eight important biopharmaceutical manufacturing documents and design documents are described and the relationship between documents is discussed.

Biopharmaceutical Manufacturing Documentation

by Yong Wang

Introduction

Biopharmaceutical processes are a series of operations performed to make drugs. These processes must comply with the current Good Manufacturing Practice (cGMP) requirements, which are regulated by the US Food and Drug Administration (FDA). These processes, using biotechnologies such as fermentation, cell culture, recovery, and purification to produce drug bulks, are the most complicated processes in the pharmaceutical industry. Biopharmaceutical processes involve many different professional backgrounds, such as industrial microbiology, cell biology, chemistry, analytical chemistry, biochemistry, and chemical engineering.

A biopharmaceutical process is usually a batch process. It may take more than a month to complete and it can involve up to 30 unit operations. Automation is used in biopharmaceutical companies extensively to increase the manufacturing reliability and to reduce the number of the operating personnel. The automatic control systems in a biopharmaceutical manufacturing company are complicated because of the complexity of the bioprocesses.

Years of practices at biopharmaceutical manufacturing made the engineers in this area believe that during biopharmaceutical manufacturing operations, manual operations must be added or combined with automatic operations. The combination of manual and automatic operations makes the biopharmaceutical process more complex.

Due to the complexity of biopharmaceutical manufacturing, the working ranges of each biopharmaceutical professional are narrowed down to small sections. Narrowing down working ranges or professional ranges requires less discipline, less training, and less experience to the working professional. It helps the professional become more focused and efficient.

On the other hand, many biopharmaceutical professionals do not have a chance to see a broader picture of the whole biopharmaceutical manufacturing process. This can cause problems because some of the roles in a biopharmaceutical company require knowledge of the whole picture. To overcome this problem, some biopharmaceutical companies or the biopharmaceutical divisions of pharmaceutical companies, often encourage people to move from position to position. This enables them to get multiple discipline training, to become knowledgeable at a broader picture, and to have the ability to foresee something before it happens.

However, it takes a long time for people to move from section to section to get the experiences and knowledge. It is even more difficult for the professionals outside of the pharmaceutical manufacturing di-

Table A. Biopharmaceutical professional's percentage time in documentation.

Profession Area	Percentage of the Working Time in Documentation
Process Engineering	30-70%
Validation	50-90%
Automation	30-50%
Manufacturing Supervisor	30-70%
Operator	20-30%
Facility Engineering	20-30%
Maintenance Worker	10-20%
Quality Assurance	40-70%
Chemical Analysis	20-30%
Chemical Analysis Method Developer	30-40%
Management	30-50%

Biopharm Documentation

vision to understand the details of the biopharmaceutical manufacturing. These professionals are the scientists/engineers who work in the R&D division of biopharmaceutical companies: the process engineers, the validation engineers, and the automation engineers who work for engineering firms or consultant companies. It may be a good idea to let these people know some details of the broad picture of how a biopharmaceutical company operates because they are involved in the various details of the biopharmaceutical manufacturing.

In this article, a process and operational documentation model for a typical biopharmaceutical manufacturing system will be presented. Some of the important biopharmaceutical manufacturing documents and design documents will be described and the relationship between documents will be discussed. The purpose of this article is to let people, who are interested in biopharmaceutical manufacturing, understand a broad picture from the angle of process engineering through process documentation activities.

Importance of Documentation

In section 211.100(a) of the FDA document: 21 CFR Part 11 (4-1-02 Edition)[1], the FDA states, "There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess." In section 211.188 of the same document, the FDA states: "Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch." Here the FDA requires a licensed pharmaceutical manufacturing company not only completely to record all the manufacturing information at the time of the performance, but also to have all the manufacturing procedures written before the operations. These written process procedures should promise the correct products to be made in the specified quality, which the pharmaceutical manufacturing company addressed to FDA in license application. All the pharmaceutical manufacturing companies, including the biopharmaceutical manufacturing companies, must comply with the documentation required to make bulk pharmaceuticals or pharmaceutical products.

Documentation is an important daily job for most biopharmaceutical manufacturing professionals. The production related activities should be documented according to cGMP and almost all the activities of the biopharmaceutical manufacturing professionals are production related. It is observed that pharmaceutical professions spend huge efforts in document activities. Table A shows what percentage of the working time a biopharmaceutical professional spends in the documentation related activities. The data in Table A is observed or estimated by the author since there is no survey data available in this aspect.

It is understandable that a high percentage of the total biopharmaceutical manufacturing salary cost is for the manufacturing documentation activity. The biopharmaceutical manufacturing documentation is extremely costly in normal situations.

It will cost more in abnormal situations. It is estimated that to a new drug, one day behind its marketing schedule may cost a pharmaceutical company up to $1 million.[2] Many of the delays can be excused on documentation because certain important documents are not ready according to the schedules. Furthermore, biopharmaceutical manufacturing companies usually use relatively large batch scale. Each batch of a biopharmaceutical product may cost millions of dollars. Mistakes in operations may result in quality problems or losing a batch. It is not acceptable for a biopharmaceutical manufacturing company to risk quality problems or to lose a batch by malfunctioning.

Figure 1. Table of Contents of an FRS for a local control system.

One of the goals of biopharmaceutical manufacturing documentation is to reduce the risk of making mistakes during operation. The method is to guide the well-trained operators through the manufacturing steps carefully using thoroughly considered and tested manufacturing procedures. Biopharmaceutical manufacturing managers spend tremendous effort on documentation for this purpose.

Since biopharmaceutical manufacturing documentation is important and costly, studying and understanding biopharmaceutical manufacturing documentation activities, and promoting the biopharmaceutical manufacturing documentation efficiency will help professionals to reduce the pharmaceutical manufacturing cost. All levels of managers in a pharmaceutical manufacturing company are directly involved in the biopharmaceutical documents' drafting, reviewing, approval, changing, and execution. A biopharmaceutical manufacturing documentation level usually directly reflects the biopharmaceutical manufacturing company's management level.

Documentation is not a very pleasant process. People, when creating documents, must be fully concentrated. Pharmaceutical manufacturing documentation requires knowledgeable and skilled people since the documentation contents, as well as formats have to meet a manufacturing company's quality standard. Documentation could also be an endless process. People can work on a document forever to improve its quality. How to create a qualified document in a limited time span or in an efficient way is an art and may involve some talent. Quality assurance personnel need to control the documentation quality at a proper level. Project managers should not underestimate the documentation efforts.

Bioprocess Engineering Strategy

As mentioned before, typical biopharmaceutical manufacturing involves a high degree of automation and also involves some manual operating procedures that include preparations or setups. There are two process engineering strategic reasons behind this fact.

Most biopharmaceutical manufacturing facilities are designed to make multiple products, and even a facility is designed for making single product, it is always expected that other products may be produced in the facility in future. Adding manual preparation steps will make the operations of the manufacturing facilities more flexible. It is noticed that a bioprocess is composed of multiple operating procedures. Each operating procedure serves its own function. The differences between bioprocesses can be expressed as which functionalities are involved in certain order. It makes process engineering easier to divide a bioprocess into the operating procedures in their functionalities even in one unit operation. It is practical and beneficial to define and develop operating procedures according to the functionalities. These functional operating procedures, after being connected using automatic or manual procedures, form the bioprocess. Since it is easier, simpler, and more convenient to use manual operation procedures for transitions between functional operating proce-

dures, manual operating procedures are used vastly for transition or connection purposes. Manual operations also give an automatic sequence a good pause point for automation development, verification, validation, and monitoring. These functional operating procedures, which contain automation sequences, after being optimized to comply with the cGMP requirements, form Standard Operating Procedures (SOPs). Breaking bioprocesses into functional operating procedures makes it possible for many people working on a linear bioprocess at the same time. It also makes bioprocess changes easy because usually a change only involves certain operating procedure(s), there is no impact on the rest of the procedures.

There is another important reason to break down a bioprocess into pieces. Any biopharmaceutical manufacturing facility involves the process phase and the cleaning phase. There is a requirement to segregate the process piping systems from the cleaning piping systems. Valves used for the separation purpose are not considered as 100% reliable. System separation using valves may fail and cause severe results. The best way for separating the piping systems is to have a physical segregation between both piping systems. Transfer panels are used for the physical segregation between piping systems. However, using a transfer panel requires manual preparations and set ups. Furthermore, operation on a transfer panel involves breaking a sealed and potentially pressured process system. For safety concern and other reasons, some of the manual valves are added to process piping systems to protect the operation personnel from energetic, chemical, and biological hazards during manual set ups or prevent potential important process piping leaks. This also requires manual operating procedures involved in biopharmaceutical manufacturing.

Process Description

Process description is the core bioprocess document to all biopharmaceutical manufacturing companies. It may be called different names by different biopharmaceutical manufacturing companies. Process description describes under certain process conditions, how a pharmaceutical bulk or a drug product is produced. It gives all the process steps and procedures in chronological order and gives the process control specifications in the different process steps. It gives the process titer range and rough recovery rate for each process step. It gives rough material balances. It gives the recipes of all the media and buffers. It not only estimates the quantities of all the materials, such as chemicals, ingredients, and solvents, involved in the process, but also gives all the quality control requirements of the raw materials. A full version of a process description may include the scientific background of process theories and the related process procedures. It also may include the summary and the lessons learned from process development. It may point out where the critical manufacturing steps are, and it may tell what will happen if the process controls are out of the specification ranges at these critical steps. For example, in a pharmaceutical fermentation process, increase of fermentation temperature

from 28°C to 30°C will increase the ratio of an unwanted byproduct, which has very similar chemical structure to the drug product and which will cause purification problems. In this case, it is indicated in the process description that although the optimum fermentation temperature control range was 28°C ± 0.5°C at the stage, once the fermentation temperature reaches 28.6°C, an alarm should be triggered to remind the process engineers and operators to pay special attention to prevent the fermentation temperature reaching 29-30°C. Otherwise, the final impurity in the product will increase up to 0.5%. A process description is usually drafted by the process development scientist/engineers. The readers of the document are the process related engineers, scientists, and managers. A process description is the most confidential biopharmaceutical manufacturing document. Not every engineer/scientist in a biopharmaceutical manufacturing company has the access to the full version of the document because of confidentiality reasons. Many people may only access a part of it. A process description is used for the process engineers and the supervisors to understand the bioprocess. It also is used for developing the main operation document and used for deciding the process control strategies, process control parameters, and the process control ranges during the design stages. Usually a process description is drafted by the scientists and engineers from the process development division according to the process summary and the developmen-

Description	Tag	IDLE Mode	RUN Mode	SIP 1 Prep	SIP 2 T<100		SIP 3 T≥100		SIP 4 Hold		SIP 5 T>100		SIP 6 100≤T	
					F	E	F	E	F	E	F	E	F	E
Media-1 relay	P-3001C	X	P	X	X	X	X	X	X	X	X	X	X	X
Acid relay (pump)	P-3001A	X	P	X	X	X	X	X	X	X	X	X	X	X
Base relay (pump)	P-3001B	X	P	X	X	X	X	X	X	X	X	X	X	X
Agitator	AG-3000	X	P	X	0	0	0	0	0	0	0	0	0	0
Exhaust	FV-020	X	0	X	0	0	X	X	X	X	X	X	0	0
Vessel drain	FV-023	X	X	X	X	0	X	0	X	0	X	0	X	X
CIP to sample valve	FV-024	X	X	X	X	X	X	X	X	X	X	X	X	X
Acid port	FV-025	X	P	X	X	0	0	0	0	0	0	0	X	X
Base port	FV-026	X	P	X	X	0	0	0	0	0	0	0	X	X
Media-1 port	FV-027	X	P	X	X	0	0	0	0	0	0	0	X	X
Jacket Blowdown	FV-029	X	X	0	X	X	X	X	X	X	X	X	X	X
CIP Header Drain	FV-034	X	X	X	0	0	0	0	0	0	0	0	0	0
Media-2/Inoc. port	FV-035	X	P	X	X	0	0	0	0	0	0	0	X	X
Circ pump	PU-3000	X	0	X	X	X	X	X	X	X	0	X	0	0
Heat	TV-050	X	P	X	X	X	X	X	X	X	X	X	X	X
Cool	TV-051	X	P	X	X	X	X	X	X	X	0	P	P	P
Glycol to seal HE	TV-052	X	0	X	X	X	X	X	X	X	0	0	0	0
Jacket glycol empty	TV-053	X	X	0	X	X	X	X	X	X	X	X	X	X
Jacket drain	TV-054	X	X	X	0	0	0	0	0	0	X	X	X	X
Sparge port trap	TV-056	X	X	X	0	X	X	0	X	P	X	0	X	X
Sparge filter drain	TV-057	X	X	X	0	X	0	0	0	0	0	0	X	X
Sparge gas valve	TV-058	X	0	X	X	X	X	X	X	X	0	0	0	0
Exhaust filter trap	TV-059	X	X	X	X	X	0	0	0	0	0	0	X	X
Exhaust drain	TV-060	X	X	X	X	X	0	0	0	0	0	0	X	X
Jacket steam	TV-062	X	X	X	0	X	P	X	P	X	X	X	X	X
Jacket recirculation	FV-063	X	0	X	X	X	X	X	X	X	0	0	0	0
Clean Steam to Header	TV-066	X	X	X	0	0	0	0	0	0	X	X	X	X
CIP/SIP to Sparge	TV-067	X	X	X	0	0	0	0	0	0	X	X	X	X
CIP/SIP to Overlay	TV-071	X	X	X	0	0	0	0	0	0	X	X	X	X
Filter Drain	TV-073	X	X	X	0	X	0	0	0	0	0	0	X	X
Key: X = Off-Closed O = On-Open NA = Not Applicable P = Pulse-Condition														

Table B. Sample of a valve matrix.

tal batch records. Process engineers from the manufacturing division also may be involved in the activity. After pharmaceutical production starts, the drug process will be continually improved or updated by the manufacturing division. The process engineer responsible for the bioprocess usually is the responsible person to update the related process description.

Process Narrative

When a biopharmaceutical manufacturing company or a potential biopharmaceutical manufacturing company requests an engineering company for a new manufacturing facility design, a document called a process narrative needs to be supplied to the engineering company. The engineering company will develop the process narrative into a Basis of Design (BOD) document through a process conceptual design.

A process narrative is a partial version of the process description. It gives as needed process information to an engineering company. It describes what is going to be made, and describes the process steps and procedures. It gives the process titer range, rough recovery rate for each process steps, and some basic material data. It gives the target of the annual yield of the facility, minimum and maximum. Usually the scientific background of a bioprocess, the tricky part of the process, and process reasons may not be included in a process narrative. Media or buffer recipes must be supplied to the design engineers for material balance calculations. Sometimes, all the supplying raw materials may be shown as material A, B, C, D, etc. in the recipe part of a user requirement for confidential reasons. Another approach for keeping bioprocess secrets is to only give out the main ingredients in media or buffer recipes. The main ingredients in recipes are very important for engineering calculation such as the material balance calculations. While the trace components of a recipe, especially a media recipe, play important confidential roles in bioprocess. Without showing trace components in a recipe, a bioprocess secret can be kept because the trace components can't be predicted or estimated. The trace components in a media recipe are the trace amount of vitamins, biotins, metals, and salts.

Different companies may call the process narrative other names, such as process description, design narrative, estimate narrative, or user requirement. An engineering company may be asked to draft a process narrative by a potential biopharmaceutical company due to lack of process engineering force. In this case, the potential biopharmaceutical company needs to provide process development summaries to the engineering company.

Basis of Design (BOD) Document

In a conceptual design, the early phase of a facility design, the process engineers digest the information in the process narrative, make the process flow diagram, and do a series of material balance and heat balance calculations. The process engineers will lay out all the process requirements to all different disciplines, such as architecture, HVAC, electrical, and environmental. The process engineers also will list the main process equipment and all the supporting utility equip-

ment. The architects will make building layouts to fit the process requirements. The project engineers will make a plan for the schedules, the milestones of the design and construction, and capital investment in certain facility scale. Different scales of facility may be laid out for the pharmaceutical company to review and to make decisions. After discussions and modifications, the finalized conceptual design summary becomes the Basis of Design (BOD) document for the facility design project. Different companies may call the BOD a scope document. The scope of a BOD varies from company to company. Some companies' BOD documents contain much more than others.

Some biopharmaceutical manufacturing companies, which have enough process engineering force, are able to do a conceptual design themselves. These companies sometimes supply a scope document, which includes a process narrative, to an engineering company for further designs.

Operating Procedure

When an engineering company submits a set of Process and Instrumentation Diagrams (P&IDs) to a pharmaceutical manufacturing company for review or further design, a set of documents called operating procedures are submitted with the set of P&IDs. Usually engineers divide the biopharmaceutical facility into many process systems during design stages according to unit operations. A process system is an equipment concept of a unit operation. Each process system is composed of the main equipment, where an important step of a bioprocess is carried out, and its related piping. A process system can be illustrated in one or a few P&IDs. Usually one operating procedure is written for each operating system. An operating procedure is a design document to describe how a process system on the P&IDs is considered to be operated by the design engineers. An operating procedure is composed of one or several functional operating procedures. All the manual operating procedures and the beginning step and the end step of an automatic operation are described in an operating procedure in chronological order.

Operating procedures are for instrumentation engineers, control engineers, or automation engineers in engineering companies to understand the process details. The process engineers or the supervisors of a manufacturing company use operating procedures to develop their SOPs. They outline the main and important operating procedures involved in the process system. It is not a good idea to spend too much time or add too many details into an operating procedure because it is drafted at the preliminary design stage. At this stage, many details have not been finalized or developed. There will be many changes afterward.

Sometimes, because of time or money, process design engineers may only walk through the P&IDs with the professionals from biopharmaceutical companies or in other disciplines of the design company without writing the operating procedures.

Operating procedures can also be called different names, such as sequence of operations or operational outline, by different companies.

Biopharmaceutical Manufacturing Control Systems

To describe biopharmaceutical manufacturing automatic control system documents, it is necessary to briefly describe the biopharmaceutical manufacturing control systems first.

All the biopharmaceutical manufacturing control systems can be considered as either local control systems or central control systems.

Local control systems are located very close to the process systems they control. Usually they are installed in the local control cabinets of the process systems. Typically, one local control system only controls one process system. The Programmable Logic Controller (PLC) system is representative of the local control systems. About 20 years ago, when pharmaceutical manufacturing automation was at its early stage, PLC was used for pharmaceutical manufacturing automation control. PLC control system using ladder logics as its programming bases. Other control systems, using other programming bases, are developed these years as local control systems. A local control system can communicate with Supervisory Control and Data Acquisition (SCADA) systems, or other control systems.

A central control system controls many process systems remotely. It also can control process systems with local control systems through the local control systems. A central control system is usually located in a central control room where the automation engineers or the operators are working in a manufacturing facility or a whole manufacturing plant. The best benefit of using a central control system is that it makes interactions between two or more process systems much easier. A Distributed Control System (DCS) is developed as a central control system. It can handle many more control devices and measuring instruments at the same time remotely. It also supplies data storage function. There are control modules imbedded into a DCS control system, which make programming easy by configuring the imbedded modules. It improves the operation efficiency by providing operators with visibility in multiple areas of a plant. One improved central control system is very popular in the biopharmaceutical manufacturing industry. It is considered a scalable process control system. The system uses Windows NT as its platform. The system communicates easier with a PC because they have the same platform. People consider it a more user-friendly system because they are more familiar with PC's

Figure 2. Sample schedule of biopharmaceutical manufacturing documentation.

platform. The system can be integrated with other control systems, which adds other functions to the system easily. The system makes it easier to track the system changes and to validate the system.

Local control systems are used for controlling such process systems as centrifuges, in which fast signal responses are very important. Local control systems also are used for some sophisticated and discrete process systems, such as fermentors and chromatography skids. Using which kind of control system also is dependent on the management philosophy of the manufacturing facility. Sometimes, local control systems have been used in a facility in which there are many process systems. In this situation, all the process systems stand separately or are less integrated and more operational flexibility has been shown. On the other hand, a central control system, due to the integration of process systems, shows better cooperation between process systems.

Whatever kind of control system is used for a pharmaceutical manufacturing facility, automation engineers require process engineers to supply detailed process instructions and the automatic process procedures, which are called automation sequences, for implementing the control systems.

Functional Requirement Specification (FRS) and Detail Design Specification (DDS)

FRS and DDS are documents involved in pharmaceutical facility control systems and automation. They are drafted at different design stages. Generally speaking, FRS specifies the process system requirements to automation. DDS addresses the solutions to the specified pharmaceutical facility control systems. These documents specify the control system infrastructures, the automation sequences, various control parameters, and the operating safety features. However, using either local control systems or central control systems, the documentation contents and formats, and documentation development pathways are different.

An FRS for a local control system specifies all the process requirements. Figure 1 is an example of the Table of Contents of an FRS for a local control system. In Figure 1, typical contents of an FRS for a PLC system have been shown. The scope and the purpose of the control system have been introduced. Chapter 3 of the Table of Contents is very important. In this Chapter, important process requirements have been specified, such as the operating modes, control loops, the Automation Sequences, I/O lists, PLC file designations, alarm/interlock information, etc. The automation sequences in the FRS are shown as a valve matrix. A valve matrix is a table, in which all the automatic valve positions or pump status in a process system are listed for all the process steps. Table B shows an example of a valve matrix. Drafting an FRS for a local control system needs efforts from both process engineers and the automation or control engineers. Engineers start to draft an FRS at the end of the preliminary design stage. A DDS of a local control system usually is an updated or finalized version of FRS. There are not too many structure changes from an FRS upgrading to a DDS for a local control system. Usually, at the end of the detail design stage or at the beginning of the

commissioning stage, people change the documentation title from FRS to DDS.

An FRS for a central control system is much different from an FRS for a local control system. An FRS of a central control system contains the scope and the purpose of the control system, the description of control loops, the automation sequences, and alarm/interlocks etc. Process engineers usually draft the FRS for a central control system. These engineers' main efforts, when drafting the FRS, is specifying the automation sequences, alarm specifications, and the interlocks. These automation sequences are shown as a descriptive format. Each complete piece of automation sequence is called a recipe or a code and is numbered or named. Recipes work with the operating procedures to complete the modern biopharmaceutical operations. DDS of a central control system is drafted by automation or control engineers in the detailed design stage. In a DDS, the descriptive automation sequences are shown as the programming language format. The automation system, the system infrastructures, the I/O addresses, and the data recording systems are specified. A DDS finalizes the specifications, process controls, alarms, and the interlocks required by the FRS.

Although FRS and DDS documents are developed by the design engineers, after turned over to a biopharmaceutical manufacturing company, process engineers are responsible for updating the FRS whenever a control system is upgraded or modified. The automation or control engineers are responsible for updating the DDS whenever the control system is upgraded or modified by the process engineers in a biopharmaceutical manufacturing company.

Standard Operating Procedures (SOPs)

Biopharmaceutical manufacturing SOPs are a group of written instructions for certain process function(s). An SOP is an accurate, clear, succinct, and detailed list of operating procedures for operating personnel. For example, if an SOP describes to open a manual valve, if the location of the valve is difficult to find, the SOP might describe where the valve is exactly located. SOPs involve operating procedures with general functions, such as CIP or SIP operating procedures. Usually, SOPs are linear operating procedures and do not involve multiple processing choices. SOPs tell the operator to select which recipe for the operation and how to select the automation recipe on a computer terminal. SOPs include manual operations and involve operating a computer keyboard or pressing buttons on a computer terminal. SOPs are developed based on the operating procedure. An SOP gives the safety instructions. Usually, an SOP is drafted by a supervisor of operations, by a process engineer, or by a pharmaceutical manufacturing consultant during the process system commissioning. An SOP is usually a small operating procedure unit. SOPs also are used to train operating personnel who are familiar with standard or general operations.

Manufacturing Process Descriptive (MPD)

The main manufacturing operation documents are called batch sheets or batch documents because biopharmaceutical

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processes usually are operated in a batch mode. Today, the same document is called Manufacturing Process Descriptive (MPD) by biopharmaceutical manufacturing companies. MPD is the main operating procedures which describes how to operate manufacturing facilities to make a drug. MPD reaches the same degree of operation details as do the SOPs. MPD involves operating procedures with specific functions. MPD involves the multiple choices' operations. An MPD is developed according to its process description. An MPD covers operating procedures for many process systems. Sometimes, some of the operating procedures with general functions are repeated for several times. One of the benefits of developing SOPs is the repeated part of the procedures can be written as SOPs. These SOPs are referred in an MPD instead of describing them several times in an MPD.

MPD are involved with the process data recorded by the operating personnel. For most of the bioprocesses, the process data will directly be recorded in the MPD according to instructions. When a process batch frequency is high, separating the process data record book from an MPD could be considered. Managers or engineers divide MPDs according to their operational functioning area. For example, MPDs are divided as fermentation MPD, recovery MPD, purification MPD, and media and buffer preparation MPD, etc. Usually, an MPD is drafted by a process engineer, a supervisor, or a combination of the two during the process system commissioning. The narrative detail degree of an MPD may vary from company to company. It takes two months to six months

to draft an MPD, which depends on how complicated and what degrees of details it reaches.

Unlike process descriptions, the MPDs will not explain why a bioprocess should be performed in a certain way.

Summary and Discussion

This article introduced a number of biopharmaceutical manufacturing documents. Figure 2 shows a typical biopharmaceutical manufacturing documentation schedule. In a facility, a central control system is to be used as a control system for the whole facility. It is expected that it will take two and a half years to establish this new biopharmaceutical manufacturing facility through designing, construction, commissioning, and validation. In Figure 2, the time lines of the documents, which are discussed in this article, have been shown. Some other documentation activities, such as FAT, IQ, OQ, and PQ, although they are not discussed in this article, are shown for comparison of the documentation time frames. Colors are used for expressing the responsible disciplines for their documents. In this way, the author hopes to give readers an overall picture of biopharmaceutical manufacturing documentation activities. Figure 3 shows a documentation information flow path to show the biophar-maceutical manufacturing documentation process geographically. In Figure 3, only partial sections of BOD and partial relationships between sections have been shown because a full discussion about BOD is not the purpose of this article. Also, in Figure 3, dashed lines are
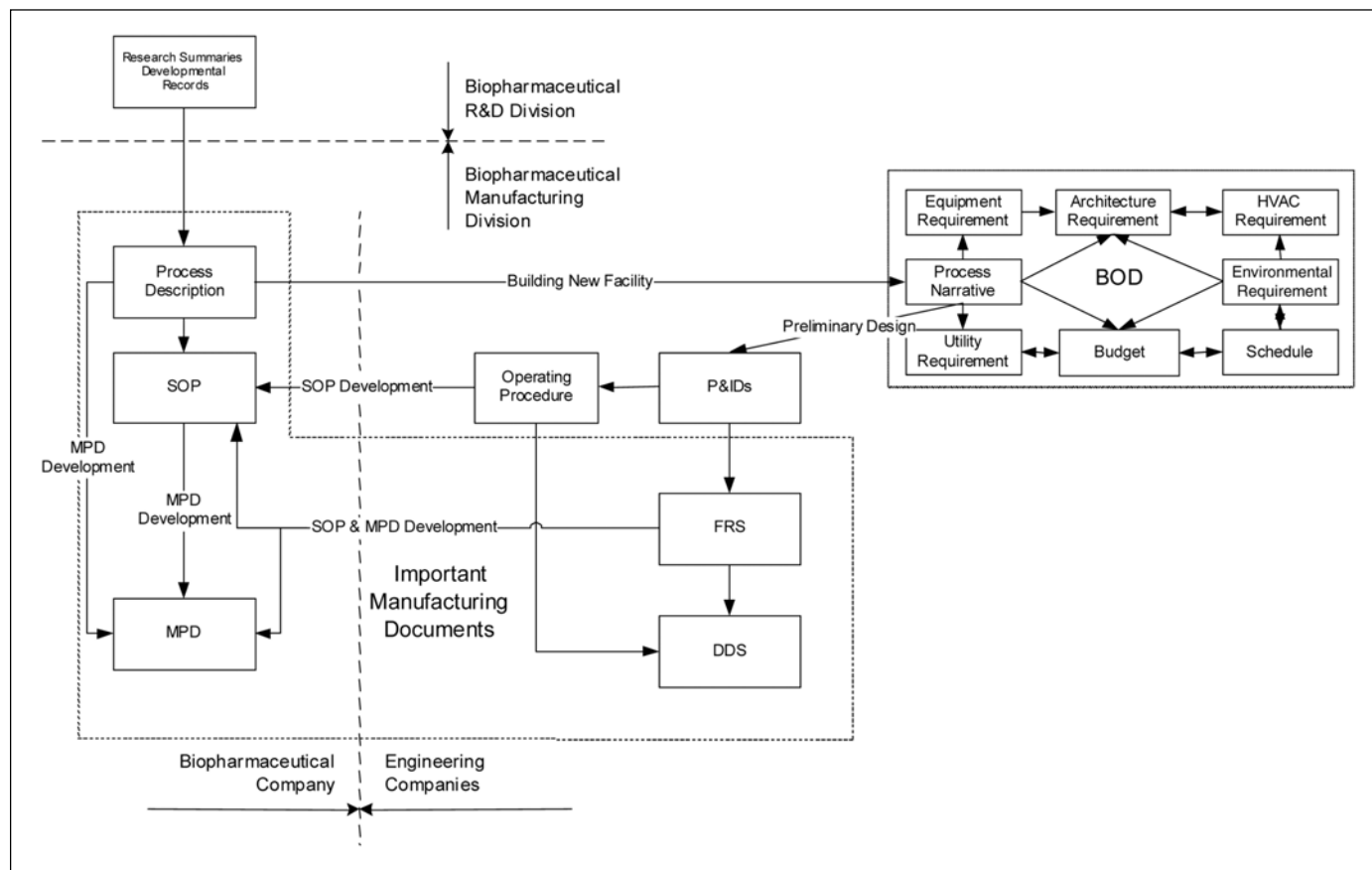

Figure 3. Typical biopharmaceutical manufacturing documentation information flow diagram.

used to specify typical responsible boundaries among R&D divisions, production divisions of a biopharmaceutical company, and engineering companies. However, sometimes changes of responsible boundaries have been seen. For example, a biopharmaceutical company can hire an engineering firm to prepare SOPs.

Process descriptions, MPDs, SOPs, FRSs, and DDSs are critical biopharmaceutical manufacturing documents. Process description is considered as the process laws or the process bible, which must be followed during manufacturing. SOPs are the block documents, which describe manual operating procedures, describe the procedures of choosing a proper automation recipe, and describe the procedures to start and end a special automatic operation. An SOP may involve one to several pieces of automation sequences. These pieces of automation sequences are referred as recipes. The details of an automation sequence can be found in an FRS as a format of process procedure and it can be found in a DDS as a programming format. An MPD describes bioprocess procedures as a whole and refers SOPs when they are needed. MPD follows the process directions from the process description. An MPD is more like a process thread, which attaches the SOPs as the blocks on the thread to form a biopharmaceutical process. Usually, SOPs cover the common process procedures, such as CIP, SIP, and typical operations. MPD covers rare process procedures, which form individual different bioprocesses. Both DDSs and FRSs related to the SOPs or MPD in two language versions to reveal the automation details. If multiple bioprocesses are involved, there will be multiple process descriptions and multiple MPDs. Multiple MPDs are more like multiple threads, which attach similar blocks, the SOPs, on them in different order and different orientations. FRSs and DDSs typically may not be changed as the related SOPs are not changed.

Operating procedures are not critical bioprocess documents. However, their existence will make it easier for the people responsible for developing SOP because an operating procedure includes the main procedures of SOPs. Usually, an Operating Procedure covers the whole range of a process system including CIP, SIP, and typical operations. However, an SOP covers one of the functional procedures, such as CIP, or SIP, or one of the operations.

BOD is a main facility design document. It gives the beginning points for a preliminary design or a detail design. The finalized FRS and DDS represent the design results.

Some problems about documentation preparation have been seen. One of the examples is people did not understand the requirement of an operating procedure. Adding much more details to operating procedures were requested. Since bioprocess details were still changing at the time, all the related detailed operating procedures had to be changed accordingly from time to time, which wasted time. Another example is that sometimes people neglect the important process engineering efforts in preparing FRSs. People thought FRSs were documents for control systems. So, only control or automation engineers were requested to complete FRSs although control or automation engineers had no problems to draft a "FRS" and specify the

hardware of the control systems. The systems would be purchased and installed on time. There would be problems at the time to run and to test the control systems because the recipes, the control software, were not ready.

Although this article talks about documentation in biopharmaceutical manufacturing, the pharmaceutical manufacturing documentation activities are similar and simple. Different pharmaceutical companies may have developed different manufacturing documentation systems because of different document development history. However, the elements which build up the documentation system, and the catch points of the whole documentation system, must be the same or very similar. For example, the automation sequences can be moved out of the FRS as an individual document after reorganization of the FRS and DDS. Some company may combine the operating procedure with the automation sequence into one document. There is an example of different documentation systems shown in another article.[3] If reading it carefully, you will find all of the important manufacturing documents described in it can be found in this article; however, they are called different names.

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About the Author

Yong Wang is a Senior Process Engineer with Jacobs Engineering Group Inc. His current job responsibilities involve the design of biopharmaceutical manufacturing facilities. He has 21 years of experience in biopharmaceuticals and biotechnology. His vast experience includes process development, process scale-up, process transfer, commissioning, facility validation, process supervision, process management, and process design. He has drafted many process documents, such as process description, scope documents, FAT, SAT, IQ/OQ/PQ, FRS, SOP, batch documents, operating procedures, and raw material specifications. He also was involved in other documentation activities. He graduated from East China University of Chemical Technology with a BS in biochemical engineering and graduated from the University of Pennsylvania with an MS in chemical engineering. He is a member of ISPE. Wang can be contacted by email: yong.wang@jacobs.com.

Jacobs Engineering Group, 3 Tower Bridge, 2 Ash St., Conshohocken , PA 19428.

This article introduces an acceptance criteria for process validation to assess the production batch under validation in terms of dosage uniformity.

Process Validation Acceptance Criteria for Solid Dosage Forms

by Pramote Cholayudth

One of the most critical issues in process validation of solid dosage forms is probably the acceptance criteria in each manufacturing step. Process validation is associated with appropriate sampling and testing with respect to *sample size*, *sample number*, *sampling frequency*, *sampling location*, *sampling procedure*, and *testing method for each particular type of samples*. In general, pharmaceutical processing steps, their corresponding qualifications, and their sampling and testing plan may be illustrated as in Figure 1.

When conducting process validation of solid dosage forms, a series of extensive sampling and testing activities has to be performed in the step of *bulk mixing* and *bulk product processing (unit dosing)* which significantly influence the product uniformity.

- Bulk Mixing: a blend uniformity is tested for tablet granulation after final blending, powder mix for encapsulation after final blending.

- Bulk Product Processing (Unit Dosing): mass uniformity and content uniformity are tested, e.g., compressed tablets, capsules.

Bulk Mixing: Blend Uniformity (BU)

In 1999, the United States Food and Drug Administration (FDA) recommended (actually proposed for public comments in a Draft Guidance for Industry, ANDA's: Blend Uniformity Analysis) an acceptance limit of 90-110% of the mean ($\bar{x} \pm 10\%$) with a Relative Standard Deviation (RSD) of No More Than (NMT) 5.0% on about 6 - 10 blend samples for ensuring the adequacy of the mixing of active ingredient provided that the blend sample size is no more than three times the dosage unit weight. This criterion is intended to apply to those products of potency less than 50 mg or products with composition of active ingredient less than 50%. The FDA later received many comments on the guidance from many sources, e.g., Pharmaceutical Research and Manufacturers of America (PhRMA), stating that the RSD criterion is not based on scientific merit, i.e., not based on statistical justification. Finally, the draft guidance was withdrawn from the Web site on May 17, 2002 after the Product Quality Research Institute (PQRI)'s Blend Uniformity Working Group (BUWG) submitted to the FDA a proposal, Blend Uniformity Recommendation on "The Use of Stratified Sampling of Blend and

Figure 1. Process validation sampling and testing plan.

Sampling is undertaken for *validation testing*, regular testing, and in-process control testing purposes throughout three key manufacturing stages - bulk mixing, bulk processing (unit dosing), and packaging. Monitoring is applied to *process variables monitoring*, e.g. process temperature, room relative humidity, etc., to see if they are within the operating control limits(* www.pqri.org).

No. of Samples	$\chi^2 0.9, n-1$ [3]	F_n	SD	No. of Samples	$\chi^2 0.9, n-1$ [3]	F_n	SD
6	1.61031	1.76220	**2.89**	15	7.78954	1.34063	**3.80**
7	2.20413	1.64990	**3.09**	16	8.54675	1.32478	**3.85**
8	2.83311	1.57187	**3.24**	18	10.08518	1.29832	**3.93**
9	3.48954	1.51412	**3.37**	20	11.65091	1.27702	**3.99**
10	4.16816	1.46943	**3.47**	24	14.84795	1.24460	**4.10**
12	5.57779	1.40432	**3.63**	25	15.65868	1.23802	**4.12**
14	7.04150	1.35875	**3.75**	30	19.76774	1.21121	**4.21**
*Calculation is based on 90 % confidence level's values to increase the SD's to account for the inevitably biased blend sample data.							

Table A. Factors for conversion between population and sample standard deviations (90% confidence level*).

Dosage Units to Demonstrate Adequacy of Mix for Powder Blend." On December 30, 2002, the final (revised) report on the recommendation was resubmitted to the FDA for approval (*PQRI was appointed by the FDA for researching scientific-based regulations, e.g., blend uniformity analysis which is under the responsibility of BUWG, a committee within the institute*).

In the BUWG recommendation, the FDA's blend uniformity acceptance criterion is still in use except that the number of samples is limited to not less than 10. To provide an alternative of addressing the RSD limit problem, a way of calculating an appropriate RSD limit is introduced in this article. Starting from the 90-110% limit and under the normality assumption, the Z scores at the lower and upper percentage points covering 95% of the area under the normal curve between the lower and upper limits (90-110%) can be calculated as follows:

$$Z = \frac{USL - \mu}{\sigma} = \frac{LSL - \mu}{\sigma}$$

Where

Z = Z score at 95% confidence (significant level with two tail, $\alpha/2 = 0.025$) = 1.96
USL = upper specification limit = 110% Target Potency (TP)
LSL = lower specification limit = 90% TP
σ = population standard deviation
μ = population mean = 100% TP

$$\sigma = \frac{110 - 100}{1.96} = 5.10\% \text{ TP}$$

The corresponding sample Standard Deviation (S or SD) for n blend samples may be calculated using the conversion factor derived by the following equation:

$$\chi^2 1 - \alpha, n - 1 = (n - 1)\frac{S^2}{\sigma^2}$$

Where

$\chi^2 1 - \alpha, n - 1$ = Chi square at 1-α confidence interval with n-1 degrees of freedom
n-1 = degree of freedom
S^2 = sample variance
σ^2 = population variance

After derivation, it can be expressed as follows:

$$\sigma = \sqrt{\frac{n-1}{\chi^2 1 - \alpha, n - 1}} S = F_n \times S$$

Where

F_n = Conversion factor for sample size n

$$= \sqrt{\frac{n-1}{\chi^2 1 - \alpha, n - 1}}$$

To make the calculation more convenient, conversion factors for some frequently used numbers of blend samples are provided in Table A.

The corresponding sample SD can be computed as follows:

$$\sigma = F_n \times S$$
$$S(SD) = \sigma/F_{n=10} = 5.10/1.46943 = 3.47\% \text{ TP}$$

In summary, the protocol limits for blend uniformity for 10 blend samples are:

- control limit (blend uniformity): mean ± 10% absolute; SD ≤ 3.47% TP

In general, the protocol limits for blend uniformity for n blend samples are:

- control limit (blend uniformity): mean ± 10% absolute; SD ≤ $5.10/F_n$ % TP

We can see that "10% absolute" is introduced in the limit. In the BUWG final report, the limit has been slightly modified from "*mean ± 10%*" to "*mean ± 10% absolute.*" For example, if the mean is 99.7% TP, the corresponding limit is 89.7 – 109.7% TP.

One fact associated with blend uniformity is sampling bias as one never takes true blend samples from the blend, i.e., segregation occurs during thief sampling under the existing technology resulting in biased or deviated blend uniformity data. Such segregation also occurs during sample handling to QC laboratory and subsequently weighing prior to assay. The two latter cases could be overcome by assaying the entire blend sample of size 1-3 times (sometimes 5 or 10 times if 1-3 times is no more practical) the dosage unit weight. So blend

uniformity is affected significantly by the sampling bias rather than weighing error or analytical error. From a research paper written by Berman and Planchard, "Blend Uniformity and Unit Dose Sampling" – "*We believe that this was due to sampling bias, and as a result, the blend specimens that were assayed were not representative of the population. …led to lower concentrations of drug in the samples than in the population. Consequently, the RSDs of the samples were biased on the high side since the sample means were biased on the low side*." Such a lower potency is explained to have been created from electrostatic charges resulting in overfilling of the thief chamber with fine powder. And that is the reason why 1) only the SD values, as above, are used instead of the RSDs, and 2) the "± 10% absolute" criterion is used to avoid the biased control limit - *Figure 2.*

In the article, the Standard Deviation Prediction Interval (SDPI) method for calculation of critical (maximum) standard deviation for blend uniformity was introduced. This method was later referred in the PDA Technical Report No. 25, *Blend Uniformity Analysis: Validation and In-Process Testing* in 1997. In the report, tabulated critical SDs are provided. For example, if n = 10, the critical SD is 3.841 where the calculation employs the equation below:

$$S_{cr} = \frac{S_{10}}{\sqrt{F_{1-\alpha, 9, n-1}}}$$

Where

n = number of blend samples
S_{cr} = the critical standard deviation for blend uniformity data
S_{10} = the upper bound of standard deviation for a sample of dosage units of size 10
$1 - \alpha$ = confidence interval (e.g. = 0.9)
F = the F statistic

The S_{cr}, maximum SD of blend uniformity data, will ensure at least 90% confidence that the content uniformity test result will pass the USP stage 1 criteria (n = 10), i.e., RSD not more than 6%. So the upper bound of the standard deviation for a future sample of dosage units (stage 1: n = 10) will be:

S_{10} = 0.06 × [target concentration] = 0.06 × 100
= 6.0% LP

Therefore,

$$S_{cr} = \frac{S_{10}}{\sqrt{F_{0.9,9,9}}} = \frac{6}{\sqrt{2.44034}} = 3.841\% \text{ TP}$$

Where

$F_{0.9,9,9}$ = 2.44034

Figure 2. Taking a blend sample from cubic blender.

The blend uniformity is sometimes tested on two (or even more) sets of samples. For example, when two sets of 10 blend samples are taken at the blending time 10 and 15 minutes respectively. The two test results will more effectively demonstrate the trend of blend uniformity rather than a single set of 20 samples' results and also help to identify the time for blend optimality.

Bulk Processing (Unit Dosing): Mass and Content Uniformity
1. Mass Uniformity
Establishing the protocol limits for bulk products with respect to the control and RSD limits for the dosage units weights, or mass uniformity, is based on both the pilot production lot data and official limits. For example, if the average sample $\overline{SD}$ for pilot production batch is 1.5% of nominal weight calculated from at least 20 samples, the standard error of the mean is $1.5/\sqrt{10}$ or 0.47 % of nominal weight where 10 is the sample size. The protocol control limit is established, according to control chart criterion, at ± 3σ about the nominal weight. So it is required to convert $\overline{SD}$ to σ using a conversion factor computed in the same manner as above, but at a higher confidence level, 95%, as shown in Table B.

In the example, the population (lot) SD (σ) will be 1.5 × 1.64520 or 2.47% of nominal weight. So the control limit for individual tablets will be 3 × 2.47 or 7.4% about the nominal weight and the control limit for average weight (n = 10) is 3 × 0.47 × 1.64520 or 2.3% about the nominal weight. However, the ± 3σ range, or ± 3 $\overline{SD}$ × F_n, must not exceed the official (USP XIX) limits, i.e., for nominal weight not more than 130 mg, the 3 SD × F_n is not more than 10% of the nominal weight, for weight between 130 and 325 mg, not more than 7.5%, and

No. of Samples	$\chi^2$0.95, n – 1 [3]	F_n	No. of Samples	$\chi^2$0.95, n – 1 [3]	F_n
10	3.32512	1.64520	40	25.69538	1.23198
20	10.11701	1.37041	50	33.93029	1.20172
30	17.70838	1.27970	60	42.33930	1.18047

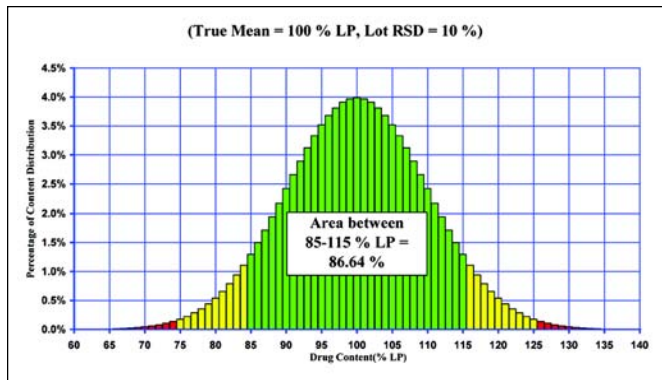Table B. Factors for conversion between population and sample standard deviations (95% confidence level).

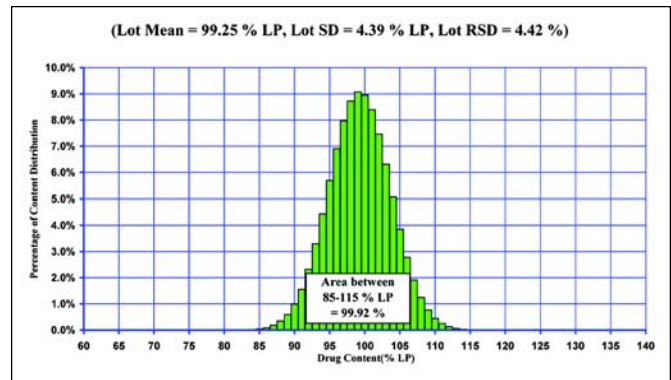Figure 3. Normal distribution curve for USP content uniformity.

Figure 4. Normal distribution curve for content uniformity.

for weight $\overline{\text{not}}$ less than 325 mg, not more than 5%. If the dosage unit weight (nominal) in this example is 125 mg/unit (≤ 130 mg/unit), the established control limit is acceptable, i.e., more stringent than the official limit.

Setting the RSD limit is based on the capability assumption (using $Cp \geq 1.0$) and the official limit for dosage unit weight. The maximum RSD for individual dosage units may be calculated as follows:

$$Cp \quad = \quad \frac{USL - LSL}{6\sigma}$$

$$\sigma \quad = \quad \frac{110 - 90}{6 \times 1.0} \quad = \quad 3.33\% \text{ nominal weight (NW) for weight} \leq 130 \text{ mg/unit}$$

$$SD_{n=10} \quad = \quad 3.33/1.64520 \quad = \quad 2.03\% \text{ NW} \; (\rightarrow \text{ RSD Limit (n=10)}: \leq 2.03\%)$$

$$SD_{n=20} \quad = \quad 3.33/1.37041 \quad = \quad 2.43\% \text{ NW} \; (\rightarrow \text{ RSD Limit (n=20)}: \leq 2.43\%)$$

$$\sigma \quad = \quad \frac{107.5 - 92.5}{6 \times 1.0} \quad = \quad 2.50\% \text{ (NW) for weight} > 130 - < 325 \text{ mg/unit}$$

$$SD_{n=10} \quad = \quad 2.50/1.64520 \quad = \quad 1.52\% \text{ NW} \; (\rightarrow \text{ RSD Limit (n=10)}: \leq 1.52\%)$$

$$SD_{n=20} \quad = \quad 2.50/1.37041 \quad = \quad 1.82\% \text{ NW} \; (\rightarrow \text{ RSD Limit (n=20)}: \leq 1.82\%)$$

$$\sigma \quad = \quad \frac{105 - 95}{6 \times 1.0} \quad = \quad 1.67\% \text{ (NW) for weight} \geq 325 \text{ mg/unit}$$

$$SD_{n=10} \quad = \quad 1.67/1.64520 \quad = \quad 1.01\% \text{ NW} \; (\rightarrow \text{ RSD Limit (n=10)}: \leq 1.01\%)$$

Data\Lot No	Lot 1	Lot 2	Lot 3	Limits
Blend Uniformity Data (% TP) - from 7 blend samples				
Sample 1	95.44	99.02	98.67	
Sample 2	95.64	97.05	96.39	
Sample 3	99.60	99.17	97.07	
Sample 4	94.54	98.88	100.40	90.00-110.00
Sample 5	98.19	95.16	99.02	
Sample 6	96.00	95.48	98.85	
Sample 7	97.34	95.51	99.82	
Mean	96.68	97.18	98.60	-
SD	1.77	1.83	1.43	≤ 3.1
Content Uniformity Data (% LP) - from 30 tablets				
Minimum	95.46	94.06	98.32	
Maximum	102.22	103.22	107.12	
Mean	99.49	100.57	100.75	USP
SD	1.88	2.20	1.91	
RSD (%)	1.89	2.18	1.90	
TP = Target Potency; SD = (Sample) Standard Deviation				
LP = Label Potency, RSD = Relative Standard Deviation = (SD/Mean) x 100				

Table C. Blend and content uniformity validation data.

$SD_{n=20}$ = 1.67/1.37041 = 1.22% NW ($\rightarrow$ RSD Limit (n=20): $\leq$ 1.22%)

In summary, the protocol limits in this example (sample size = 10) are:

- control limit (individual weight): 100 ± 7.4 or 92.6 – 107.4% NW with an RSD $\leq$ 2.03
- control limit (average weight): 100 ± 2.3 or 97.7 – 102.3% NW

General expression for mass uniformity acceptance criteria:

- Individual weights for sample size n:
  - Control limit = $100 \pm 3.\overline{SD}.F_n$ % nominal weight
  - RSD $\leq X/(3. F_n)$ %
- Average weights for sample size n:
  - Control limit = $100 \pm 3.(\overline{SD}/\sqrt{n}).F_n$ % nominal weight

Where
$\overline{SD}$ = average SD calculated as % nominal weight
F_n = conversion factor for sample size n
X = tolerance value in official limits e.g. 10% for nominal weight $\leq$ 130 mg/tablet provided that the $3.\overline{SD}.F_n$ value is no more than the tolerance value X%.
n = Sample size

A successful capability study on the tablet compression machine, for example, should have been carried out prior to evaluation of the pilot batch data so that setting the protocol limit is accurate enough.

2. Content Uniformity (CU)

The official limit of 85-115% Label Potency (LP) is determined. In the USP content uniformity acceptance criteria, the sample RSD limits, i.e., NMT 6.0% for sample size 10 and NMT 7.8% for sample size 30, are based on the lot RSD of NMT 10% [7,11]. One may calculate a corresponding RSD for sample size n using conversion factors in Table B as follows:

From the relationship,

σ = $F_n \times S$
If σ = 10% LP (i.e. Lot RSD = 10% assuming the lot mean equals 100% LP), $F_{n=10}$ = 1.64520
$SD_{n=10}$ = $\sigma/F_{n=10}$ = 10/1.64520 = 6.08% LP (See USP's)
If n = 30, $F_{n=30}$ = 1.27970
$SD_{n=30}$ = 10/1.27970 = 7.81% LP(See USP's)
If n = 60, $F_{n=60}$ = 1.18047
$SD_{n=60}$ = 10/1.18047 = 8.47% LP

Since a validation sample size is generally larger than that specified in the USP, e.g., PQRI requires at least 60 dosage units in the first stage, the RSD (8.47%) corresponding to USP's acceptance criteria may be computed as above. But the USP concept of lot RSD, i.e., 10%, provides only 86.64% of
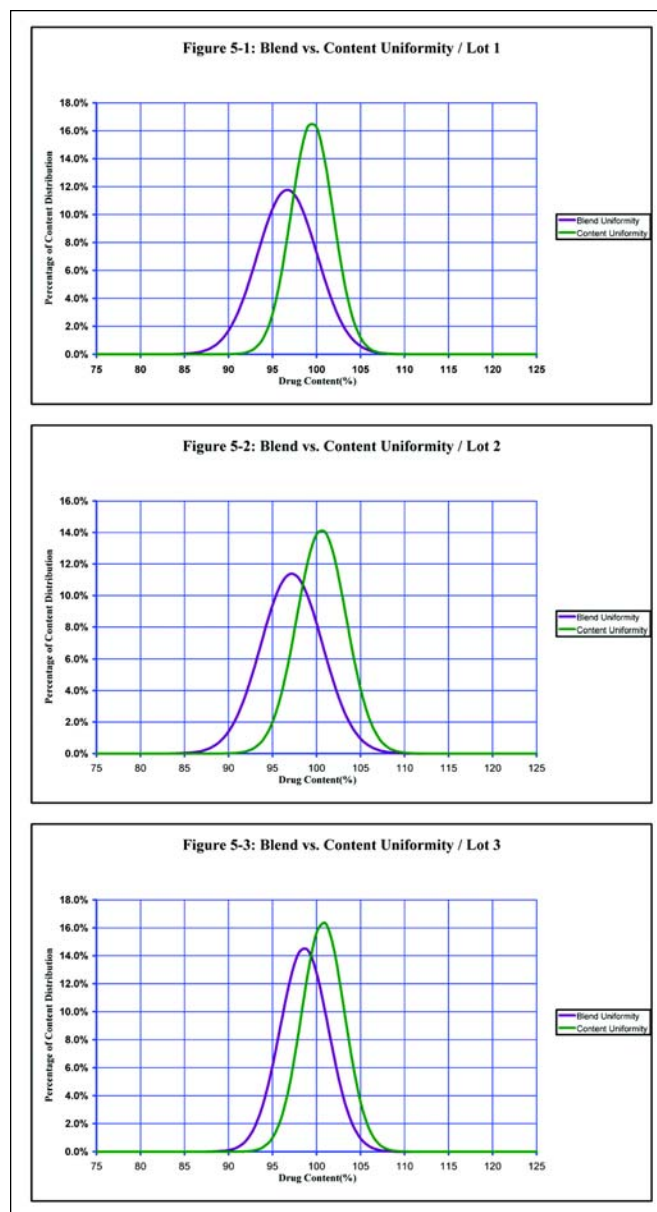

Figure 5. Distribution curves for blend and content uniformity for the three validation lots.

dosage units of the entire lot falling within the range of 85-115% LP (see calculation below, Figure 3).

In establishing a more stringent RSD in a validation protocol, the percentage of dosage units falling within the content uniformity range of 85-115% LP may be designed, for example 99%. Then the corresponding lot RSD is calculated and finally the sample RSD. To demonstrate how the lot percentages and RSDs above have been derived, one should start with calculation of the Z scores at lower and upper limits as follows:

$$Z = \frac{USL - \mu}{\sigma} \quad (\text{or} = \frac{LSL - \mu}{\sigma})$$

Where
Z = Z score at 95% confidence (significant level, $\alpha/2 = 0.025$) = 1.96
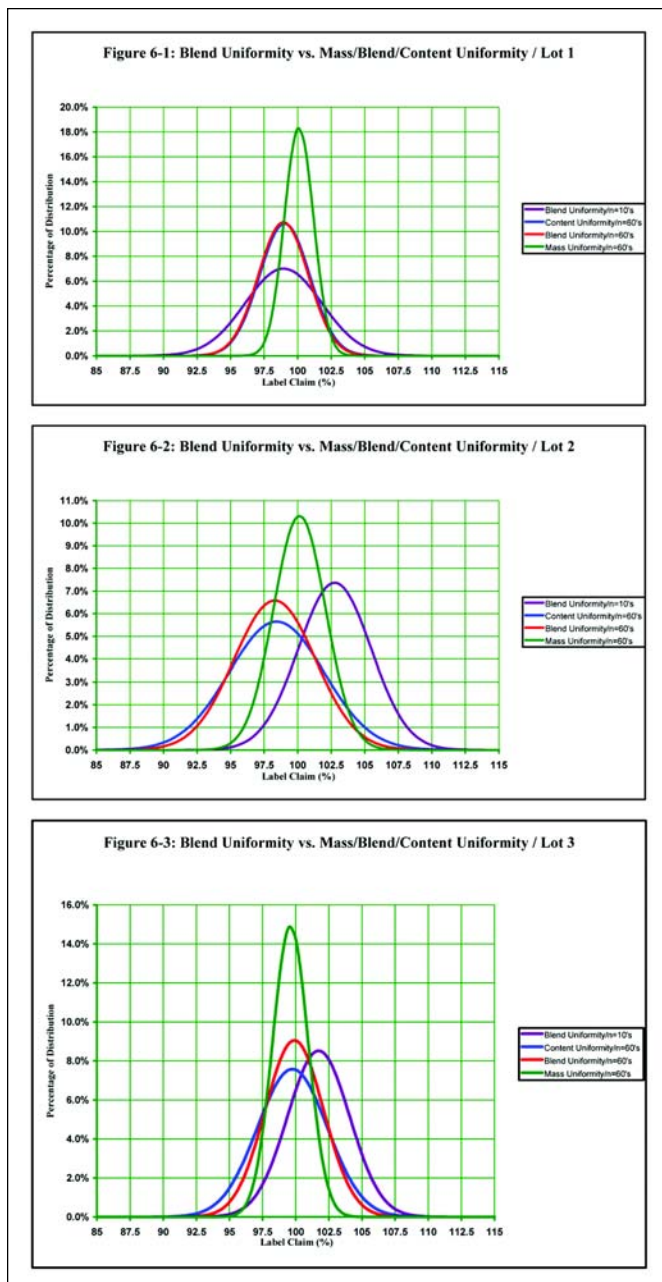
Figure 6. Distribution curves for blend uniformity and mass/blend/content uniformity.

USL   =   upper specification limit   =   115% LP
LSL   =   lower specification limit   =   85% LP
σ =   population standard deviation   =   10% LP
μ =   population mean   =   100% LP

$$Z \quad = \quad \frac{115 - 100}{10} \quad = \quad 1.5 \text{ (upper side)}$$

So in the case of the two-tailed curve, the Z scores at 85 and 115% LP are -1.5 (probability 0.0668) and 1.5 (probability 0.9332). The percentage of the area between 85-115% LP is 0.9332-0.0668 or 86.64% (for USP criteria).

For 99% acceptance criteria, imply that $\alpha/2 = (1-0.99)/2 = 0.005$, $1-\alpha/2 = 0.995$, the Z scores at 85 and 115% LP are $-2.5758 (\alpha/2 = 0.005)$ and $2.5758 (1-\alpha/2 = 0.995)$ respectively.

The percentage of the area between 85-115% LP under the normal curve is 0.995-0.005 or 99.00%.

To find the lot RSD is demonstrated as follows:

$$\sigma \quad = \quad \frac{115 - 100}{2.5758} \quad = \quad 5.82\% \text{ LP } (\rightarrow \text{ Lot RSD} = 5.82\%)$$

If n   =   30, $F_{n=30}$ =   1.27970

$SD_{n=30}$ =   5.82/1.27970 = 4.55% LP ($\rightarrow$ Lot $RSD_{n=30}$ = 4.55%)

If n   =   60, $F_{n=60}$ =   1.18047

$SD_{n=60}$ =   5.82/1.18047 = 4.93% LP ($\rightarrow$ Lot $RSD_{n=60}$ = 4.93%)

In summary, the protocol limits for content uniformity of sample size n at conforming rate of P % of dosage units falling within 85-115% LP range are:

- Control limit: 85-115% LP
- $RSD \leq 15/(F_n \times Z_{0.005P+0.5})$

Suppose a protocol requires, for content uniformity, sample size of 60 units at conforming rate of 99% (of dosage units falling within 85 – 115% LP), the RSD limit will be 4.93%, if the results are that the mean of 60 units is 99.25% and RSD is 3.75%. One can calculate the actual conforming rate as follows: $\sigma = 3.75 \times 99.25 \times 1.18047/100 = 4.39$, $Z_1 = (115-99.25)/4.39 = 3.58479$ (probability 0.99983), and $Z_2 = (85-99.25)/4.39 = -3.24338$ (probability 0.00059). The actual conforming rate P = 0.99983-0.00059 = 0.9992 or 99.92% - *Figure 4*.

As discussed earlier, the blend uniformity data may be biased due to several factors. Therefore, blend and content uniformity data are often not correlated. The following is a comparison of blend uniformity and tablet content uniformity in terms of numerical data and graphical presentations from the same batches showing how blend uniformity is often not predictive of the overall batch uniformity. Such data were recently generated during a prospective validation of a tablet product containing 8% of active ingredient and compressed into 125 mg/tablet where 7 blend samples and 30 tablets were taken from each lot and witnessed by the author. The PQRI sampling plan was not issued yet at the time of execution. A status of sampling bias in the blend uniformity data may be observed, i.e., most of the individual results are below 100% TP - *Table C*.

Those sample statistics in Table C may be estimated through statistical methods to be the corresponding population (lot) parameters and presented as distribution curves in Figure 5 series. From the presentations, it is obvious that the BU curves for all the three lots are biased (deviated) on the same side, i.e., always shift from the CU curves to the lower side. From the BU curves, there is a tendency that individual blend samples, if taken in the future, may have the assay result exceeding (below) the lower limit. All the CU curves are very steep showing an excellent degree of meeting the specifications as their tails (lower and upper) lie far from the lower and upper limits, i.e., 85 and 115% LP.

The magnitude of bias or deviation from the true value for each individual result is not always the same so it is possible that the results do not meet the protocol acceptance criteria, either control limit or SD limit, while the content uniformity results are excellent. In this case, it doesn't mean that such a validation trial fails, but it still passes provided that an investigation has to be undertaken and documented on the validation report.

3. Blend Uniformity Evaluated from Dosage Unit Data

An alternative way to assess the blend uniformity is recommended by PQRI under the concept that a tablet compression machine or capsule filling machine is an excellent tool for blend sampling, i.e., feeding blended granules into the machine dies and then compress or feeding blended powder into capsules respectively. When each dosage unit's weight is checked prior to assaying, blend uniformity data, or *weight-corrected* data as called in the PQRI report, can be obtained in addition to content uniformity result using the same sample's data. The advantages of using dosage unit samples instead of blend samples are explained in the PQRI's recommendation report, e.g., eliminating the blend sampling error, accounting for segregation after blending, etc. Such blend uniformity data will provide an assurance that the entire lot of blend is uniform (at the time of unit dosing step). The PQRI's acceptance limit for blend uniformity, using 60 dosage units, are between 90-110% TP for each sampling location mean with an RSD, for 60 weight-corrected units, of NMT 6.0% which is corresponding to the lot RSD of 7.08% using the same conversion criterion as above. The lot RSD 7.08% will provide about 84.22% of the lot falling within the range of 90-110% TP.

To demonstrate the calculation, $Z = (110-100)/7.08 = 1.4124$ (upper side) so the Z scores at 90 and 110% LP are -1.4124 (probability 0.0789) and 1.4124 (probability 0.9211). The percentage of the area between 90-110% TP is 0.9211-0.0789 or 84.22%.

The advantage of blend uniformity evaluated from dosage units (tablets) over that from the blend samples is its capability to demonstrate the overall batch uniformity as evidenced by the following example. At the time of final review of this article, the author has witnessed a protocol execution of a hormone tablet product with active ingredient 0.75 mg per 100 mg of tablet. The protocol was designed to fully follow the PQRI sampling plan (10 blend samples for blend uniformity and 60 tablets by stratified sampling for content uniformity testing) and acceptance criteria. Fortunately, all three validation batch results are available in time and can be summarized in graphical presentations in Figure 6. Here is another example demonstrating that blend uniformity (blend sample) is not always predictive of batch uniformity.

From preliminary evaluation, the blend uniformity curves (red) generated from tablet data (weight-corrected data*) are at about the same location as the content uniformity curves (blue) while the blend uniformity (blend sample) curves (violet) have no repeated patterns, i.e., inconsistent in both location (mean) and spread (variability). Such, the blend sample

curves are always wider (longer tails) and create no predictable feature of the overall batch uniformity. Each mass uniformity curve (green) will demonstrate how adequate control of tablet compression can provide an excellent content uniformity and also demonstrate, with excellent mass uniformity, an interesting characteristic between the blend (weight-corrected) and content uniformity.

*Note: Weight-corrected data is content uniformity data transformed into a nominal tablet weight database. For example, if 2 mg active ingredient in 120 mg per tablet is nominal, and the assay result for a tablet is 1.990 mg active or 99.50% label claim (= (1.990/2) × 100) in 119 mg tablet weight, the weight corrected value is 99.50 × 120/119 = 100.34% target potency.

Conclusion

The criteria for establishing validation protocol limits for a pharmaceutical process are based on statistical techniques, e.g., using process capability or Z score under normality assumption. The database used for establishing the protocol limits may be derived from two sources 1) official limits, e.g., content uniformity, and 2) historical product data to establish the natural and statistical limits, e.g., dosage unit weights from the pilot production batch. The criteria related to official limits are slightly different in application in establishing the blend and content uniformity limits. For blend uniformity, the calculated lot sigma is converted to the corresponding sample standard deviation depending on the number of blend samples. No RSD limit is established for blend uniformity under the reason of sampling biased data. While the content uniformity still follows the official control limit (85-115% LP), but employs a more stringent RSD instead of 6% depending on the established conforming rate and the number of dosage unit samples. The criteria related to historical data are beneficial for setting more stringent control limits for mass uniformity, than the official limits. This article focuses on the quality attributes with respect to the active ingredient uniformity; however, the other key attributes, e.g., size distribution data, product assay, dissolution rate, etc., also are taken into account in process validation.

To ensure that the established protocol limits are valid, it is recommended that a few pre-validation batches are produced to have the key process parameters characterized prior to establishing the limits. A successful process validation is the outcome of a successful process, i.e., a process with high accuracy (the lot mean approaches target) and high precision (the lot standard deviation approaches zero). The sampling plan with respect to the sample size and sampling location is another key issue for successful process validation as the larger and more representative the samples, the less biased results.

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About the Author

Pramote Cholayudth is a Production Director for Biolab, Co., Ltd., a leading generic drugs manufacturing company in Thailand. He is a guest speaker for Process Validation, held for industrial pharmacists, sponsored by the FDA, in addition to being a guest lecturer for GMP, Validation, and Special Problems in Industrial Pharmacy in several universities. He was previously a full time lecturer in the School of Pharmacy, Department of Industrial Pharmacy in a private university for four years (1998-2001). Prior to entering the academic arena, he spent 23 years in the pharmaceutical industry with Bayer Laboratories (1974-1981) and OLIC (Thailand) Limited (1981-1997). Cholayudth is the author of *Concepts and Practices of Pharmaceutical Process Validation* which has been reviewed by the university's academic committee. He can be contacted at: tel: +662-709-3121-2 ext. 3080, fax: +662-740-9586, or e-mail: cpramote2000@yahoo.com.

Biolab, Co., Ltd., 625 Lane 7A, Bangpoo Industrial Estate, Muang, Samutprakarn, 10280 Thailand.

This article discusses the benefits of portal applications for centralizing critical electronic data, application requirements and essential features designed to support 21 CFR compliance.

Electronic Documentation - The Rewards of Information and Proactive Implementation

by Glenn Schulz and Gerhard Werling

Introduction

Anyone keeping an eye on the US Food and Drug Administration (FDA) has undoubtedly noticed the Agency's continual changes to the scope and application of Part 11 of Title 21 of the Code of Federal Regulations; Electronic Records; Electronic Signatures (21 CFR Part 11). In February 2003, the FDA issued a notice that it would re-examine 21 CFR Part 11 and make new recommendations on requirements for validation, audit trails, record retention, record copying, and legacy systems. In the meantime, despite any changes the FDA is considering to 21 CFR Part 11, adhering to internal documentation standards and implementing an integrated electronic document and change management system can enhance your process, manufacturing, and help you address future regulatory challenges.

Only time will tell what the final 21 CFR Part 11 regulations will look like, but those pharmaceutical manufacturers who are headed down the electronic documentation path shouldn't view the FDA's re-engineering as a reason to halt the process. For those of you moving forward, this article will discuss the benefits of portal applications for centralizing critical electronic data, application requirements and essential features designed to support 21 CFR compliance. It also will touch on the specific requirements for and benefits of validation, audit trail, and security - three of the most critical issues surrounding regulatory compliance. Lastly, it will outline practical applications of MES environments and workflows.

Proactive Strategies for Centralizing Electronic Data

With the ever-growing list of manufacturing information systems comes an increase in IT and engineering support. Regardless of the benefits achieved through validation, audit trails, record retention, etc., many manufacturers simply don't have the time or the resources to manage and support so many individual regulatory-supporting applications.

In an effort to manage all these information applications, companies are starting to look at centralizing plant-wide information, applications and project files. Instead of multiple independently managed applications, portal-type applications now allow companies to funnel all the information they need through one main resource. Information can be gathered directly from intelligent devices and through the software applications that manage and audit change, prevent and predict failures, and verify validation status of current projects.

Portal applications offer an array of benefits, including:

- Companies can control program usage across the board.

- Companies can manage access to all files, projects, and products.

- Companies have a record of all (and most current) program versions running.

- Companies have a record of accepted configurations and programs running.

Electronic Documentation

- Managers know when changes are made to all systems designated to be tracked.

- Managers know who made changes or why they were made.

- Companies can effectively run validated programs or regulated programs.

- Companies have records of all changes made to devices, applications, and project files being tracked.

- Operators can match programs and devices to safeguard production.

- Companies can prevent unwanted changes from occurring to devices, applications, and project files.

- Companies can restore previously used programs and correct invalid program changes in case of unauthorized changes.

Centralizing information does require an application that provides all the components needed to gather, store, manage, and report information from disparate sources. Key components include:

- Central server - the main server should manage services, databases, modules, and clients for the entire system. This central server requires fail-over provisioning to prevent a single point of failure within the system.

- Event log - an event log is the centralized data repository and interface providing services that help store and display warnings, errors, and informational messages. Event log functionality requires the use of an application that captures events and pushes the information to the event log.

- Audit log - the audit log is a centralized data repository and interface used to store and display edits occurring in manufacturing products. Audit log functionality requires the use of an application that captures events and pushes the information to the audit log.

- Service monitor - typically a server-based feature, a service monitor feature can allow users to monitor the state of services running on any workstation or server.

- File management - a file management system allows users to restrict and record the file usage. It should protect intellectual property and manage validated programs by requiring users to check in and out of the system. It can manage version history, making sure that changes made to files are recorded and stored.

- Backup, recovery, and verification services - backup, recovery, and verification services should support scheduled data uploads and compares to devices and files. Some products offer built-in device support for controllers and other manufacturing hardware, but open driver support also should be available, providing third party device and software support.
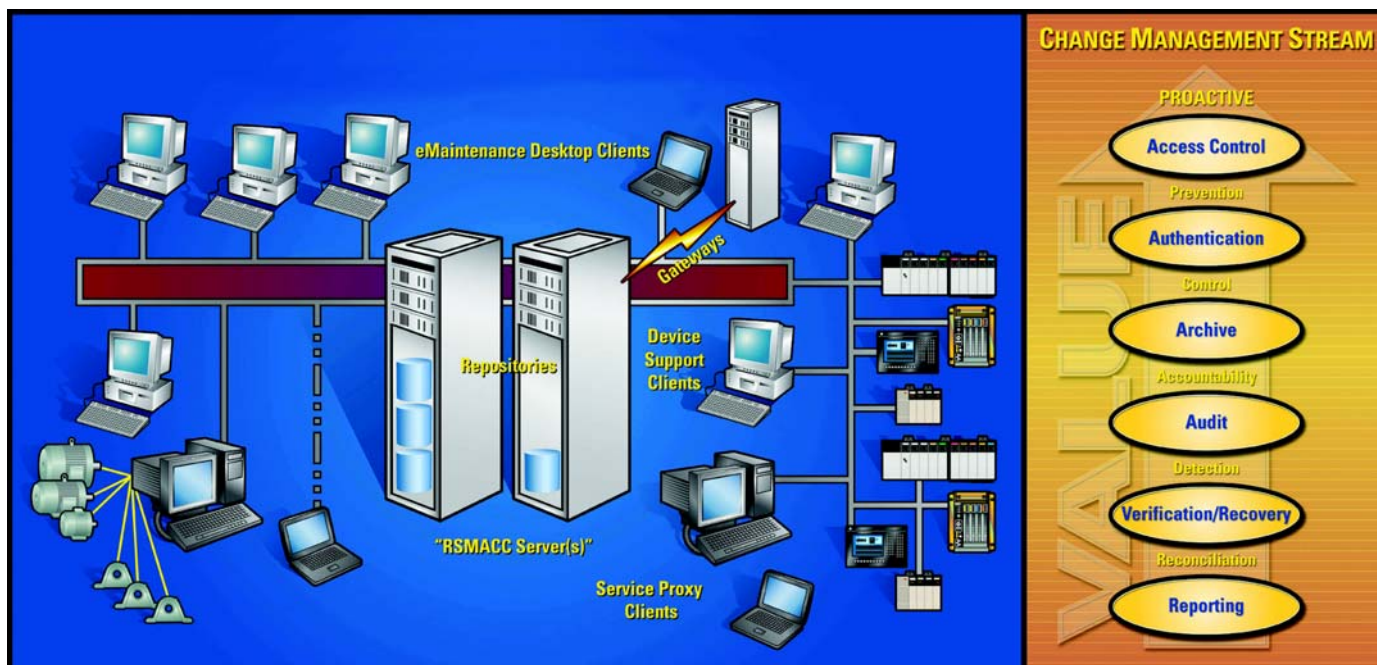

Figure 1. In an effort to manage critical information, companies are using portal-type applications to funnel plant-wide information through one main resource.

- Security - a security server or other security features should be available to provide the ability to create rules of usage of products and specific product actions based on user and workstation names. In addition, some of the more robust change management solutions offer additional levels of security that take into consideration not just who is accessing the system, but where they're accessing it from and what they're making changes to.

- Client - the client interface should allow users on networked workstations to access server functionality – to control, display, search, and view capabilities for event and audit databases, secure access to products and specific features in products, and license check-in and out.

- License manager - product activation can be managed through a license manager to manage optimum concurrency, restricted usage, historical usage information, license check-out status, and license location.

Validation

With data centralized and a portal application in place, companies can focus on applying the features that will support future regulatory requirements. The first is validation. The FDA's Quality System regulation for the manufacturing of medical devices, which was published in the Federal Register on October 7, 1996 and took effect on June 1, 1997[1] requires that "when computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use according to an established protocol."[2]

Validation of manufacturing software and systems implies that the actions taken by the user or the system itself (as when automated) have been executed with the proper legal authority and formalities. Regardless of future FDA modifications to validation requirements, validation of pharmaceutical manufacturing systems is still extremely important – as it is required by the predicate rules (e.g. Parts 210/211). Proving the accuracy of one's manufacturing process, docu-

Figure 2. Audit trail information should identify changes made to the system, including the user and the reason for the change.

ment changes made to the system and identification of invalid or altered records is not just a matter of Federal regulation, it's a matter of company liability.

To achieve computerized system validation and electronic records, a portal application should be able to automatically run functions that support the on-going evaluation of the manufacturing process on a regular schedule. Routine - but critical - operations like programmable logic controller uploads, file backups, and compares can be set to run automatically at scheduled times. Important aspects of an effective validation system include:

- the ability to run multiple events simultaneously, such as upload from several controllers at the same time

- automatically detect altered files and projects

- automatic notifications to operators when changes or alterations are detected

- built-in driver support for multiple controllers

- built-in support for third-party devices and products

- reporting capabilities

- security

A portal application such as Rockwell Automation's electronic maintenance documentation and change management application is designed to centralize, manage, and maintain information for system validation. It can act as a central data-access point for audit trail, file management, and product license tracking information, making it a multi-purpose solution for pharmaceutical manufacturers tracking and using various data points - *Figure 1*.

Audit Trails

Another important function for any pharmaceutical manufacturer is the use of audit trails and the storage and retrievability of records created by a system. An audit trail is a secure, computer-generated, time-stamped report that independently records the date and time of operator entries and actions that create, modify, or delete electronic records. Although they make up only part of 21 CFR regulations, audit trails offer substantial benefits to manufacturers, especially pharmaceutical, chemical, food/beverage or consumer products manufacturers – companies whose end products are used for human consumption. Most importantly, audit trails can protect manufacturers in cases involving:

- *Individual accountability* - an individual's actions are tracked in the audit trail making users personally accountable for their actions. This helps to deter users from circumventing security policies or making unauthorized changes to manufacturing systems. Even if users do act

outside policy or authorization, the actions captured in the audit trail can help identify the user for accountability.

- *Events reconstruction* - in the case of unplanned downtime, machine failure, or other problems, audit trails can be used to reconstruct events after the problem has occurred. Depending on the level of information collected, the extent and amount of damage occurring from an incident can be assessed by reviewing audit trails of system activity to pinpoint how, when, and why the incident occurred.

- *Problem monitoring* - Audit trails can be used as real-time tools to monitor manufacturing processes and/or problems as they occur. Based on the information being gathered through the manufacturing process, real time monitoring can help detect process inconsistencies, machine failure, over-utilization of system resources, or energy outages.

- *Intrusion detection* - Intrusion detection refers to the process of identifying any efforts to penetrate a manufacturing or enterprise computer system and gain unauthorized access. Often, this access can originate within the company although external security breach attempts also are common. Audit trails can only help in intrusion detection if they record appropriate security events.[3]

Despite the overwhelming benefits of audit trails, the ability to effectively archive and retrieve data in a reliable, secure form is where many current systems fail to deliver. In the pharmaceutical industry, audit trail reports should be generated for *all* user actions on *all* manufacturing devices and systems. At the very least, audit reports must identify changes made, the user, and the reason for the change. Audit records entered into an audit trail are typically identified with the following: (Figure 2)

- time stamp recording the transaction time

- the kind of transaction (create, delete, modify)

- affected field name

- old value of the field

- new value of the field

- identification of the user who performed the transaction

Additionally, the following information can be added for each data change:

- the reason for the change, whenever appropriate

- an electronic signature, whenever appropriate

Once made, audit trail records and the data they report must be protected from alteration or deletion, and information owners/managers should be able to easily identify unauthorized changes.

Security

Because security is such an important aspect of electronic record keeping, all electronic records must be stored in a secure location and format. Electronic records are often kept in a relational database, such as the Microsoft SQL database. However, keep in mind that database tables should be locked within the database, and access to tables restricted through secure layers. Some products use Microsoft Windows and Microsoft SQL security. An effective validation and audit trail system also should prevent end users from modifying records, further protecting the company against liabilities due to possible information sabotage. For information reporting, users can often choose from a variety of reporting tools including reports within validation system software or separate tools, such as Microsoft Access, Microsoft SQL Server tools, or Crystal Reports. Keep in mind that these separate reporting tools are not 21 CFR compliant, as data can be manipulated by the user. Only reports generated from archived data and protected from end user intervention or manipulation will adhere to 21 CFR requirements.

Applying Electronic Documentation in the Facility

Once you understand the history and benefits of an integrated electronic document and change management system, how can it be effectively implemented? Data within a pharmaceutical company can be referenced as Standard Operating Procedures (SOPs). SOPs, which come in all types of forms and varieties, including bills of material and production procedures, need to be version-controlled. Today's advanced Manufacturing Execution Systems (MES) allow SOPs to be managed electronically. SOPs are usually written with a Microsoft Word-compatible editor, and are created in three common ways:

- start with an existing SOP template (often called a Master SOP), and make the necessary additions

- make a copy of an existing SOP and edit accordingly

- build an SOP from scratch

Word-compatible editors allow SOP developers to work in a "normal" office environment and use common editing features, while at the same time have the necessary document (version) control.

SOP approval requires the MES system to have a document workflow that is well-defined based on the company's policies. These rules can be effectively enforced through the MES system using its version control features. The systems may use a version graph function that reflects the approval

workflow assigned to each SOP object according to company and GMP rules. In addition, electronic signatures can be attached to each workflow step to assure proper authorization.

For example, an employee in quality assurance can create a new SOP (from a template, an existing SOP, or scratch) and then initiate the approval review. The type of review is of course dependent on the type of SOP with more significant SOPs (such as those for master validation plans) requiring higher-level approvals. A draft SOP might first go through a peer review, then quality management, then departmental management, and finally plant management if required. Each review (and in many cases corresponding electronic signature) is documented in the version history. The system enforces that only proper organizational roles may be involved in this workflow, thereby ensuring compliance to company procedures.

An SOP within the MES system also can be hyperlinked to a respective step within a production procedure. In this way, each employee can always have direct access to the valid version of the SOP that relates to the step they are executing. By double-clicking on the screen, the employee can quickly bring up the SOP – a useful tool also for in-process control activities. More advanced MES systems also allow users to query the system to find only deviations from the standard in an executed batch. As such, the quality management group in an enterprise may focus attention on these deviations. Version control features allow any data objects to be controlled by a version graph similar to the one used for SOPs – tracking creation, review, approval, valid use, and archiving.

It's often advisable for an enterprise to perform a documented risk analysis of required audit trail data to streamline management. In a risk analysis, every relevant data record created or modified by the system receives an assessment of its GxP criticality – more specifically, you need to ask if the data has a direct impact on the product quality or quality documentation. Moreover, only data that can be changed by an operator via the normal user interface need to be subject to audit trail. The change management and MES systems should be set up to capture this key audit trail data and make management of that data much more efficient.

Conclusion

Despite the uncertain future of FDA regulations on electronic records and signatures, it seems clear that the ROI benefits of integrated electronic documentation and change management are enough to propel its advancement in pharmaceutical manufacturing. At the very least, companies get a head start on some of the regulatory compliance mandates that will likely resurface within the year. At the most, companies can start paving a path to collaboration and information sharing, improve and increase workflow efficiency, and ultimately find cost-savings through information.

In addition, companies need to recognize that even more significant benefits can be derived from weaving electronic documentation into the bigger disciplines of automatic policy enforcement and overall maintenance management. Therefore, looking at electronic documentation as part of a broad automated policy enforcement strategy can compound its benefits. This broader abstraction calls for the ability to control, monitor, and enforce activities through the intersection of who (user and group), where (the current locale of the user), and what (the source and target). This simply wouldn't be possible using manual methods.

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About the Authors

Glenn Schulz became Director of Global Business Development for Rockwell Automation in 2003. He is responsible for new product development, business alliances, and strategic acquisitions under the Rockwell Software brand. Schulz began his career with Rockwell Automation in 1995 as a senior reliability engineer. In 1996, he was promoted to supervisor, product development. Schulz became manager, Product and Business Development, in 1997 and held this position until his current assignment. Schulz earned a BS in electrical engineering from the University of Wisconsin-Madison. He be contacted at tel: 1/414-328-2150 or email: gbschulz@ra.rockwell.com.

Dr. Gerhard Werling is the Director of Quality Management and Validation Services for Propack Data GmbH, a business of Rockwell Automation. Head of his department since 1994, Dr. Werling acts as Propack's quality representative and manages validation projects, consulting, and services for computerized systems. Dr. Werling is active in the GMA/NAMUR working group "Validation of Process Control Systems" and is a member of both PDA and the ISPE GAMP Forum. Dr. Werling studied computer science and mechanical engineering at Karlsruhe University in Germany, and attained his doctorate at the Institute of Process Control Systems and Robotics of the University of Karlsruhe. He can be contacted at tel: +49-(0)721-9650-835 or email: gw@propack-data.com.

Rockwell Automation, 1201 S. Second St., Milwaukee, WI 53204.

This article discusses the importance of Standard Operating Procedures (SOPs) in a regulatory environment and makes suggestions as to how to create, maintain, and circulate these documents in a manner compliant to worldwide regulatory agencies.

Effective Standard Operating Procedures in a Regulatory Environment

by Erica Charlton

Introduction

Regulatory agencies the world over, and specifically the US FDA, require the existence of a document repository to demonstrate that procedures and processes in Life Science Manufacturing facilities are in place and followed by all personnel. If a procedure or process directly affects a product, then it should be outlined in a current and approved document. Creating and maintaining a collection of these does not have to be a major headache if it is approached in a logical manner as shown in some of these basic guidelines.

Standard Operating Procedures are the explicit written description of a Production, Quality Assurance, Materials Management, Administration, Documentation, or Engineering operation performed by personnel in a GMP environment. An 'operation' is an activity which may affect the product conformance to specifications or regulations. The SOP defines the essential steps, their sequence, and precautions necessary to uniformly repeat performances of the operation.

FDA regulations require that procedures be documented, which will be audited during an FDA inspection. There are no precise instructions provided by the FDA as to how SOPs are written, stored, circulated, approved etc. It is the discretion of the regulated company how SOPs are handled. In an audit, the FDA is simply looking for the existence of these procedures and that the SOP and the associated personnel training maintains and strengthens cGMP systems, processes, and procedures.

From 21 CFR Part 211.100 (Current Good Manufacturing Practice for Finished Pharmaceuticals, Subpart F; Production and Process Controls, Written procedures; deviations):

(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.

Initiation of an SOP

The following are several events that can initiate the requirement for a new SOP: a new piece of equipment, a Corrective Action Preventative Action (CAPA), a Deviation report, a Validation requirement, a company policy change, or a change in an affiliated document.

Writing SOPs

When creating a new SOP, the 'documentation department' (or the company's equivalent) issues a unique number to the author. Logically, the best author for an SOP is a qualified individual who may or may not be the same individual executing the procedure. At the minimum, the SOP should be reviewed by someone who performs the procedure so they may have their input with regard to the accuracy.

It is important that the wording in the SOP content be clear and concise. Minimize the opportunity for discrepancies and avoid flowery, descriptive text - just get to the point. It's not a literary contest.

It's safe to assume that there are probably as many variations in SOP format and chosen headings as there are companies using them. Some may include more or less and the chrono-

logical order can vary, but the following is a list of headings from SOP templates in many Life Sciences companies:

Purpose - this is a brief statement of one or two sentences stating the reason for the SOP. It may read something like: "The purpose of this SOP is to outline the procedure for the care and maintenance of instrument x."

Scope - By writing the SOP, what do you hope to accomplish? What does this procedure apply to? The author states in the scope how much of the procedure is outlined in this SOP and what is not covered.

Responsibility and Authority - here the author indicates who, by position or title, should be responsible for learning and executing the procedure. This helps to determine who should be trained on the procedure.

Environmental Issues - this section is sometimes included in SOPs where there is the use of chemicals that could pose an environmental threat. Here it is appropriate for alerting the reader about the seriousness of chemical spills, harmful gas releases, and how to handle them. It's not necessary to rewrite the entire procedure for handling chemical spills. If there is a potential for chemical spills, there should be a separate SOP for the proper clean up. The author may refer specifically to this SOP by number in this section or under the Associated Documentation heading.

Safety - this section alerts the reader if extra care is needed when executing the procedure and what personal protective equipment is required, if any.

Associated Documentation - here the author cites instrument manuals, refers to additional SOPs or in-house documentation, corporate procedures, or additional documents cited in the body of the SOP which might overlap or enhance the information included in the SOP.

Definitions - these are simple word definitions for terms that the author feels require clarification. Acronyms are included in this section, if applicable.

General Outline - the general outline can be used to index the text in the procedure usually by the main headings. It's most helpful in long SOPs where the readers are looking for specific information. Using the General Outline they can find information quickly.

Procedure - this is written for use as a training tool. This is the step-by-step sequence of events. Additional equipment, tools, or chemicals are referred to by name. The author should identify additional documentation and contact positions if applicable.

Appendices - these are attached diagrams or separate charts, tables, and or tools that enhance the text portion and that readers may require to fully comprehend the procedure. Figures should be numbered and titled appropriately.

Training - although it is up to the author, some companies require a short collection of test questions in order that documented training systems and the SOPs can be linked. Answers are found in the body of the SOP and if the trainee has read the procedure thoroughly, they are not difficult to answer. Multiple choice, true/false questions are quick and uncomplicated. The test answers can be completed by the reader/trainee at the time of training to test the reader's ability to comprehend the procedure. This is a satisfactory method of creating a measurable training record for employees if a company chooses this method.

Miscellaneous - Some companies may include a 'Frequency' heading if it is a cleaning procedure or maintenance procedure to indicate when the procedure is required.

The SOP Format

Each company develops their own in-house method for the categorization of SOPs and the format of the SOP body, but the style should be consistent across all departments. For companies with a large index of SOPs, they will find it useful to group the documents by department, for example: all Quality Assurance SOPs are grouped under a common prefix code, the same for all Manufacturing SOPs, or Administrative SOPs. The categorization can be further defined with some form of a logical alphanumeric code, again, under the discretion of the company.

The SOP template should include somewhere; the company name, the current date, and a statement with something to the effect that: "In printed form, this document is only valid on the date shown." Which is a method of identifying uncontrolled documents. This will be expanded upon later in this article.

An SOP cover page should include; the title of the SOP, its unique number, the effective date, the author (by job title), the approver(s) (by job title), current version number, revision numbers, and the revision history if applicable.

Within the body of the SOP, it is effective to create a numbering scheme for each heading that can be a drill down sequence in each section. For example,

```
1.0  Title
     Subtitle

2.0  Title
     2.1  Subtitle
     2.2  Subtitle
          2.2.1 Subtext
               2.2.1.1  etc.
```

Of course, the tab settings are optional, but it can create a tidy looking appearance.

Approving SOPs

When a draft SOP is completed, it is circulated to the appropriate personnel for review. Approvers review to ensure the document properly reflects the procedure. It's possible (or maybe probable in some organizations) that discrepancies could cause the document to cycle around more than once for adjustments before a final copy is ready for approval. Hopefully, this can be addressed quickly to keep the process moving.

Be aware if any changes impact another part of that particular (or another) SOP and address those changes immediately.

The Document Manager (or similar position), from the Quality Assurance department, completes the final review of the SOPs. This person applies the effective date and launches the SOP from the 'draft' to 'approved' status and then live. Training for appropriate personnel should be arranged shortly thereafter.

Uncontrolled Documents

Many facilities store a complete collection of bound hard copies of SOPs at a specified location in their facility. It is important to note that any printed copies outside that location are classified as uncontrolled documents. The problem the FDA sees with hard copies is the possibility that any given SOP could be under revision (unknown to all personnel), and so the hard copy is no longer the current and valid copy.

Only current and approved versions of SOPs should be accessible by personnel. Draft versions or those under revision should be only accessible to authors and reviewers, and they are launched into the live system only when approved.

SOP Maintenance

Companies permitting hard copy collections of SOPs will have an SOP on 'How to Write SOPs.' This would be an author guideline and describe the information that should be listed under each section heading, how versions are addressed, how the SOPs are circulated for approval and launched into the live system, how to eliminate the risk of uncontrolled documents by including a print date on the hard copy SOP and the clause 'valid only on date printed.'

An electronic document management system makes the most sense for writing, circulating, and maintaining the SOP collection, and like any computer system that affects cGMP, it must be capable of audit and validation.

At a minimum, SOPs should be reviewed once every two years. Updates or revisions are completed as needed and the training-tracking database can flag appropriate personnel for timely training/retraining. It may not always be the original author available to review, but it should be someone who performs the procedure described.

A revised SOP is circulated for approval and posted on the live system in the same manner as an original copy, but the numbering scheme for the document must somewhere indicate that it is the subsequent version of the original. A note under the 'Revision History' heading should briefly summarize the changes made, by whom, the date, and the previous SOP version number that it replaces.

Old versions of SOPs should be archived for an audit trail, but should not be accessible in the live system as they are Uncontrolled Documents when out of date. An FDA auditor can request proof of existence of previous versions of any documents and proof that the company can identify any changes made through the history of the document's existence.

When SOPs become obsolete, they must be removed from the live system. In some cases, the company chooses a numbering system with almost an infinite number of possibilities whereby a number would never be reused. In other cases, the SOP number is retired for a predetermined amount of time, after which retired SOP numbers can be reissued for a new SOP. The retirement period is determined by the company policy.

The document management department is responsible for keeping the SOP library in control in that there aren't duplicate procedures being written by different people at the same time. To minimize the library, it is wise to compile multiple short procedures into a larger SOP if they are related. Be reasonable when creating SOPs. Decide which procedures warrant an official document. If the procedure affects the product in any way, then it is a GMP issue and should have an SOP to accompany it. An electronic document management system should be able to flag SOPs that are up for review and by whom.

There are dozens of commercially available applications that will effectively maintain SOP documents electronically. A search on the Web will yield many applications with the same basic components. Choosing one depends on the features and functions required by the company.

Training Personnel

The FDA requires that all personnel must have instantaneous access to approved SOPs in their work environment whether in electronic form or a controlled hard copy version, so that they may refer to the steps of any procedure at any time.

From 21 CFR Part 820.25, Quality System Regulations, Subpart B; Quality System Requirements, Personnel:

(a) General. Each manufacturer shall have sufficient personnel with the necessary education, background, training, and experience to assure that all activities required by this part are correctly performed.
(b) Training. Each manufacturer shall establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities. Training shall be documented.

And, also from 21 CFR Part 211.25, Current Good Manufacturing Practice for Finished Pharmaceuticals, Subpart B; Organization and Personnel, Personnel Qualifications:

(a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to

enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current Good Manufacturing Practice (cGMP) (including the current Good Manufacturing Practice (cGMP) regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with cGMP requirements applicable to them.

In a GMP environment, the simple existence of an SOP does not indicate (to the FDA) that personnel are trained on the procedure and therefore qualified to do his/her job. There should be a system in place by which an employee signs and dates a document indicating they have indeed read and understand the procedure. This document becomes part of the training file.

Employee retraining is not required if the changes to an existing SOP have no effect on the on-going procedure.

Some companies opt for a more advanced method of ensuring that employees have absorbed information included in the SOP that enables them to perform the job correctly, consistently, and safely. The training effectiveness becomes measurable. For example, test questions whereby the correct answers create a score. The training system must be capable of audit and validation. This is why it is advisable, in this situation, to link the SOP document system with a training tracking system. Training tracking applications can be quite sophisticated and contain lists of students, courses, schedules, instructors, classrooms, student information, course history, and course results. They are used for scheduling training and maintaining employee training files.

A training tracker application operates on a pyramid of requirements and must allow for SOPs to be linked to jobs, jobs must be defined in terms of skills, and skills must be defined in terms of teachable elements. This kind of breakdown leaves little room for ambiguity in employee's skill sets.

In addition to the drill down pyramid structure, another advantage to an electronic training tracking application is to create consistency across an organization as to when and how personnel are trained. The system administrator of the system can flag user profiles to indicate when retraining is due, arrange for training, and maintain results of training. When SOPs are revised, retraining for appropriate personnel is required, and the training tracking software should be able to notify of this if they are integrated systems.

The administrator of the training tracking software is often the company's training coordinator. Within the application, they are able to assign SOP reading lists to all employees, accompanied with an expected completion date. Personnel will access the live SOP systems to read their required SOPs and complete the training questions for each. Answers to the test questions can be recorded electronically or submitted as a hard copy, and forwarded to the training coordinator for review. The coordinator updates the employee-training file.

There are dozens of software applications which can effectively manage employee-training records and an internet search will yield many possible choices.

In conclusion, SOPs are a necessity. Follow these rules in a GMP environment:

- **What requires an SOP?**
  A procedure that affects the products' conformance to specifications or regulations must have the steps captured in an SOP document.
- **When are SOPs written?**
  SOPs should be written when there is need for a new procedure. They should be reviewed periodically and revised as needed.
- **Where are SOPs stored?**
  The most efficient method for storage and revision is an electronic document management system which makes them accessible by all employees. There also may be hard copy versions that are strictly maintained.
- **Who writes SOPs?**
  The experts are responsible for writing the SOP, in other words, those who perform the procedure. The Quality Department approves SOPs.
- **Why SOPs?**
  SOPs are necessary because the FDA says so. Ultimately, they are for the protection of everyone: employees, the employer, the public. It's just plain smart business.

References

1. American FDA, Code of Federal Regulations 21 CFR Part 211.100, Current Good Manufacturing Practice for Finished Pharmaceuticals, Subpart F, April 1, 2002.

2. American FDA, Code of Federal Regulations 21 CFR Part 820.25, Quality System Regulations, Subpart B, Quality System Requirements, April 1, 2002.

3. American FDA, Code of Federal Regulations 21 CFR Part 211.25, Current Good Manufacturing Practice for Finished Pharmaceuticals, Subpart B, April 1, 2002.

About the Author

Erica Charlton is the Marketing Representative at PENSA Technology Solutions Inc., a privately owned Canadian company which is uniquely qualified to plan, design, implement, and validate enterprise solutions for regulated manufacturing industries. Charlton holds a BSc from the University of Guelph, Ontario, Canada, and has 4 years of Quality Assurance Lab Experience in the pharmaceutical and food industries. She has been with PENSA since July 2001. She can be contacted at:

Pensa Technology Solutions, Inc., 18 King St. W., Brockville, ON, Canada K6V 3P6, tel: (613) 345-7295, email: erica_charlton@gmps.com.