Session 1: Quality Systems/Quality Management

Moderators:
Marijke Korteweg, EMEA and
Joyce Ramsbotham, Solvay Pharmaceuticals, Netherlands / EFPIA

Session 2: Risk Management

Moderators:
Tim Marten, AstraZeneca, UK and
Greg Guyer, Merck, USA

Session 3: Drug Development / Quality by Design/ Manufacturing Science/ Process Analytical Technology

Moderators:
Fritz Erni, Novartis Pharma AG, Switzerland
Michael Wierer, EDQM

Session 1: Quality Systems/Quality Management

Introduction

The main goal of the sessions on Quality Systems and Quality Management was to generate a high level of interaction amongst the participants aiming to answer three central questions of the day:

- How can we achieve the vision (ICH meeting Brussels July 2003)?
- What is the current problem?
- How can it be solved?

Population definition	% of all participants
Total number of participants = 121	
% participants - in industry	82
% participants - regulator	11
% of participants - consultant	7
% of participants having a Quality System	77
% of participants having a continuous improvement programme	55
	% of industry participants
Drug Products producer	83
API producer	60
Biotech company	27
Medical devices	7
Excipients producer	6
Vaccine producer	2
Vitamins/minerals/nutritional	2
Consumer health care	2
OTC producer	1
Analytical products	1
Are you a local EU company?	4
Are you a global company?	82
Are you a generic manufacturer?	12
Are you a R&D based company?	80

Presentation

The session was initiated by providing the audience with a brief overview of the current state of affairs in the industry. More specifically attention was focused on the vision created at the Brussels ICH meeting (supported by both industry and regulatory representatives), 'the pain' that industry feels concerning they variety of requirements which are the result of regulators regulating locally and manufacturers manufacturing globally.
Furthermore, the current and desired situation for industry was stated. The question whether or not the desired situation can be reached using GMP was presented indicating the aspects of quality management which are lacking in GMP. This question led to the kick-off of the discussions, fed by five other questions posed on the overhead.

What are your thoughts?

1. what are the problems which could be solved by this QS initiative?
2. what are the pros and cons of harmonizing?
3. what needs to be done?
4. what are the priorities?
5. how do we get from: current state to new state?

Conclusions

Change management

Put change back in the hands of industry. (statement from FDA).

Changes can be made without approval after industry has demonstrated scientific justification and fitness for use for the patient. When the auditor comes in, he can check that. Changes should be reported periodically for example in an annual report.

Robust Quality System needed to get less regulatory scrutiny.

Regulators would give industry the freedom to make changes without prior approval based on a quid pro quo of a robust quality system and scientific expertise.

Integrate reviewer and inspector so that every change is pre-approved.
(i.e based on evaluation of product, science, risk management and company)

Inspection is a spot check, a system approach instead of a product approach gives a better overview of the company. License a company based on system approach.

Changes are allowed without prior approval if processes are low risk, low complexity and the company has demonstrated good conduct.

How risk is managed is more important in the evaluation than the potential risk of the product and the process.

Companies having robust quality systems and with a good record could be allowed to make changes without prior approval of each individual change. (EU law requires prior approval of changes, but prior approval would be given via the certificate of good conduct – agreed by an EU regulator)

Discussion required in ICH on:

- what needs to be reported, "do and tell", what needs to be pre-approved
- response times for authorities to react to changes should come down and be harmonized.

- use of compatibility approach
- change control protocol (as in EU guide on near infrared)
- periodic (annual) report requirements.

Change approval should be at the level of API manufacturers themselves.

Industry puts too much detail in the dossiers. We should focus on things that are critical, notify changes on these critical aspects which affect patient safety and on what is important for the customer. Industry needs to characterize its product but in biotech it is hard to characterize molecules. Industry should justify to regulators the critical parameters.

What is the kind of information that the regulator should continue to monitor?

The EU variations guide was intended to allow industry to make changes more easily but in fact industry experiences it (very strongly) as added bureaucracy and making changes more difficult.

We need to distinguish between MA (marketing authorization) and Manufacturing License changes.

Continuous improvement

Change management is only related to products and processes. Continuous Improvement envelops more, including systems, facilities, complaints, audit follow up, trending, deviations, employees etc.

There is no attitude of improvement in industry as a result of GMP, which is a list of do's and don'ts and therefore blocks continuous improvement.

Industry does not recognize its own inconsistencies. It should develop a scorecard in its Quality System to measure these.

Continuous improvement could be the key to widening specifications, setting and changing interim specifications, reversing specification limits, by the application of statistics to results and specifications. How about thinking about specifications from another perspective? What benefit can industry get from more advanced statistics?

Scientific rationale would open the door for continuous improvement.
Evaluation of whether there is a true product risk and how frequently that risk occurs would demonstrate where improvements need to be made.

Where is the pain, what needs to be harmonized?

Industry needs to establish where the issues are between the different regulations. Focus on "what" and not on how.

Think not only what could be added, but also what can be removed. (comment from a regulator)

It is harder to comply with two regulations (US-EU) having different demands that conflict. It takes more money as the company defaults to one system which covers all (that is extremely conservative) for all sites/plants.
Examples:

- rebuilding plants to comply with different requirements for water at high cost without added value for customer

- clinical drives directive Clinical trials out of Europe as to be in compliance is very hard.
- 10years ago it cost a company £100.000 pounds for every product to keep dossiers up to date. It must be much more now and the figure probably does not include hidden costs.

It is tragic that guidelines for aseptic processes are not harmonized between the US and EU.

Rewrite factors that can be of influence instead of writing specifications. IS hard, US says there must be flexibility.

Harmonization leads to overregulation. Applies only to new products.

Regulators should get together en should decide which guidelines should be harmonized.

The concept of the qualified person is seen as a great strength of the EU system.

Trust, confidence and dialogue

What does industry have to do to gain the trust of the regulators? Generating trust between industry and regulators is critical.

High risk products will get high scrutiny from regulators.
Assessors do not know what is critical, industry does know but does not demonstrate/explain this very well.

Manufacturers should dare to break the circle of fear by questioning perceived wrong decisions by regulators. But who will start - Industry or regulators? Concrete steps from both sides are necessary to gain trust.

Industry should start the debate if they feel that an inspector has disadvantaged them or has misinterpreted guidelines. Do not just complain.

There must be the possibility to reason with inspectors in a reasonable fashion.
Regulators should be aware of international cultural differences.

Cultures amongst regulators and industry should allow dialogue.

EU regulators are very open and can be reached. They want to hear where they are not in compliance with their own regulations.

Consistency of regulators can be achieved by training/benchmarking.

We need to involve the EU Commission in our discussions.

Involvement of all industry

The interest of the different branches within the industry can be different but take them all on board (OTC, generic etc)

Detail and harmonization of guidelines

Express principles "what" in guidelines, the how is industry freedom.
Leave out details (guidance is not law), use common sense.

Guidance should not be too detailed, it will block the industry if this is the case.

Small companies do not have the resources to find the scientifically sound solutions – they want more guidance to help them.

Eliminate unnecessary requirements from GMP –do not add extra requirements.

Industry is very differentiated, resulting in the need for flexibility and less detailed guidance. Regulators must allow for different interpretations.

Guidelines should be less detailed – guidelines should be written by industry as they have the practical experience.

If regulators want to introduce a change in regulation or write a new guideline, they should directly harmonize this change or new guideline. On one hand we try to harmonise via ICH, while on the otherhand the number of guidelines which are not harmonized increases (Mopping up with the tap open.)

Compare US and EU guidelines (for instance on sterile products) and turn the two into one.

There is a lack of transparency in EU on comments received during consultation period. Comments made on guidelines do not appear to be followed up in the EU. Industry does not feel their suggestions are being used to their maximum effect.

Regulators should mutually recognize each other.

Are there gaps in GMP

Management responsibility and management commitment are missing from GMP's, which is a prerequisite for risk management.

There is a disconnection between responsibility for product quality and responsibility for the quality system.

Total R&D is left out of GMP – a solution would be to implement a quality system in R&D, bringing scientists into the Quality Assurance department, provide a training program for the R&D department which clarifies the effect of decisions made in the development stage on the quality of the final product.

Good scientific practices is the term R&D could use for these activities. R&D departments do not like to be policed. Allow science to drive the quality of work with client based thinking.

Existent GMPs can give us a complete Quality System. They contain all necessary aspects – it just depends on your interpretation.

Industry does not recognize its own inconsistencies. It should develop a scorecard in its QS to measure these.

Mutual recognition

Philosophical problems between EU and US regulators are present. Therefore acceptance of foreign acceptance reports is difficult and harmonization will not be easy.

Start with a little MRA for low risk companies with good management of potential risks.

This will help to build up trust and confidence between regulators

Session 2: Risk Management

Introduction

The purpose of these sessions is to gain input and elicit discussion on harmonization on some topics concerning risk and risk management. This harmonization is necessary to create a better understanding of risk management between the industry and regulating bodies. Through this harmonization and the sharing of knowledge, risk management decisions can be better understood and transparent.

First of all, some general points were made about the topic:

- The people from the industry, which are attending this congress (industry, regulators, producers, generics and over-counter industry) are all willing to change, but not all other stakeholders may be ready for these changes. But from a historical point of view, changes have always started in the "larger markets", so a start has to be made somewhere.
- Currently, risk assessment is unstructured, or as someone suggested: "We need a risk assessment-culture"
- Authorities at this moment do not focus on the main issues when it comes to risk assessment.

The structure, followed in these sessions, will be according to the sheet "ICH Issues to be resolved" by Greg Guyer.

Terminology, including definition of quality
A harmonization of the definitions used is important for a better dialogue between the industry and regulators. First we have to have a framework of methodology for the whole industry. After that, it can be tailored for the different set of values, either on society or on patient level. Therefore the scope of the initiative has to be clearly defined.

Everyone agrees on the fact that we do not need to "reinvent the wheel". We do not need a new system, but just effective communication.
A commonly used definition is that of ISO, so the question is: "Is this definition fit for use for the drug industry?"

Risk

- The general definition of "risk" is acceptable, but it may have to be tailored, to be applied to different processes.
- Economic risks are missing in this definition.
- It is important that already wide accepted definitions exists. The interpretation of the definition should be linked to a specific scope.
- Some discussion was on the topic whether or not the term "harm" should need defining.

Risk Assessment
This discussion was mainly about the fact that in the definition, the term "values in society" is being used.

- Some people would rather see this term being replaced by "patients (or customers)", because that is where the focus would have to be. When the focus is laid upon the patient/customer, this will work as a driver for the industry as well as for the regulators. Society should be seen as the whole of patients/customers.
- The economic risks for the producers are missing in this definition
- How to judge acceptance of risks?

- Which stakeholders are involved?
- Different perceptions of risks in different countries could lead to different decisions.
- The words *available information* could be insufficient.

Quality
- The problem occurring in the definition of Quality is the question: "How can we incorporate specific needs of the patients/customers?"
- Also in this definition the scope is a very important issue.

Consensus among the participants was on the fact that quality needed to be quality as defined by the patient/customer.
Missing in the definition of quality are the following aspects:
- Fitness for use
- Need for conformance to registered specifications
- Compliant with GMP

The question that remains is: "Should the definitions be general or specifically for the pharmaceutical industry?"

Types of Industries who use Risk Management
The first point discussed in the sessions was about other industries which already have much experience with Risk Management.
The participants came up with the following primary industries:
- Aerospace
- Food
- Banking
- Safety/Environment
- Insurance
- Medical devices
- Automotive

After naming these industries, emphasis was placed upon industries who had similarities to the Pharmaceutical Industry. The reason for this is the fact that we have to be more specific about things like the implementation of attributes and the decision making processes of these industries. We have to find out what the common thoughts / ideas of these industries are about risk management.

Some experts in these fields were discussed to look if there are possibilities for knowledge transfer.
A few were mentioned:
- British Quality Foundation
- University of Maryland in the U.S.
- There is a contact in the nuclear industry

In comparing the different industries, a few important questions seem to appear:

"The team should not reinvent the wheel."

"Which direction do we want to pursue when it comes to risk?"
When we want to emphasize low costs, we can look at the food industry. When we want to emphasize quality, we could take a look in the direction of for instance the nuclear industry.

"Should risk management be a separate function or should it be integrated in the whole process?"

Principles for effective application and consistent integration of Risk Management into product quality decisions and impact on the patient.

- Workforce has to be adequately trained to use risk management tools in decision making.
- Clear roles and responsibilities have to be defined in terms who is responsible for analyses and decision.
- Apply right tool for the right task/situation.
- Only apply Risk Management when it has value.

Operationalisation of the integration of Risk Management into the decision making process

Comparisons with other industries:

- To come to a harmonization, we don't want just a subjective method, based on purely empirical results, but also with a scientific background.
- The HACCP approach is very effective. An example was the food industry.
- Another approach is FMEA where mapping of the total process by the whole team determining what are important steps and what are not. In other words: define high and low risk points.

Currently in use in a company in the drugs industry:

- Scientific approach. Building a model through incremental steps by assembling date and using this data for input.

Key areas where formal Risk Assessment can help:

- Change control
- Defining critical parameters
- Validation Areas
- Recalls
- Significant deviations

Defining Risk Management principles for application throughout the product life cycle

One of the main questions on this topic is whether the measures should be on a mandatory basis or on a voluntary basis.
The participants agreed on the fact that voluntary basis has the greatest advantages. Show regulators the industry is in control of its systems.
To achieve this position, the whole system has to be a flexible one, because of the changing environment. The system has to be able to differentiate risk and be simple.

Information exchange

The industry and regulating agencies have a common goal: safe and effective products for patients.

It is important that they understand each other's business, for instance both parties could benefit from a shift from filing assessments to inspection of change management.

Information exchange between all stakeholders involved is crucial for this process to work. Information and names of experts in different industries (including the pharmaceutical industry) could be e-mailed to: Peter Gough, Pete.g@lilly.com. Perhaps these persons could participate in an Expert Working Group (EWP).

Incorporation of risk into resource allocation decisions

Of course it is important that all stakeholders are involved into resource allocation decisions meetings as in Noordwijk aan Zee are a real help.
An important issue is the degree of incorporation of the industries Risk Assessment approaches into the practices of inspector agencies.
Finally, it would be a relief to the industry when low risk processes are recognized by regulatory agencies as low risk thus allowing lower regulatory scrutiny.

Session 3: Drug Development / Quality by Design/ Manufacturing Science/ Process Analytical Technology

Discussion on PAT

- The definitions of PAT and PAC were discussed. The main point is that PAT leads to better understanding of the process. This information tells what adequate controls are necessary. Without understanding the underlying science, no meaningful controls can be expected. The term PAT was found misleading since the term "analytical" is of less importance than the process understanding.

- In the biotech industry PCT and PAT are already widely used tools. Also for chemical reactions PAT is used to steer to the desired end-point. PAT in Pharmaceutical production is at present not very wide spread.

- Why to apply PAT?
    - PAT is a tool to accumulate process understanding.
    - The business interest is more in reducing waste and rejects, streamlining the logistics and resources rather than reducing or eliminating end-testing of products.
- What are problems that may be encountered when using PAT?
    - Huge amounts of data are generated with PAT. The difficulty lies within the conversion to knowledge. The question is how to store the enormous amounts of raw-data. Is this necessary?
    - Statistical approaches for OOS-handling for large sample sizes are needed.
    - There is no guidance from the regulators how to submit PAT generated data.

- The group agreed that there is no need for higher quality of pharmaceuticals. However a more consistent quality leading to less rejects and recalls should be achieved (6σ process).
- The use of PAT should be kept optional for new and old processes. The companies should be able to choose.
- PAT is not only attractive for big innovator companies but may also be economically attractive for small companies and generic companies.
- Many aspects of PAT are not new. Within the new philosophy of PAT, companies have a very high expectation to get regulatory relief mainly in the area of post approval changes.
- In the context of PAT it is necessary to decouple the process of setting specifications from assessing manufacturing capabilities.

- Specifications should not only reflect process capabilities but should be based on safety and efficacy requirements.

- Are indirect measurements capable of indicating compliance with specifications and are specifications on the long run needed at all? If it can be demonstrated that indirect measurements are correlated with the specifications they maybe considered as acceptable. The conclusion of the discussion showed that specifications are needed as clear description of the desired quality.
- At present the PAT instrumentation is mainly in-house-developed. It is expected that more and more commercial equipment will be available. Calibration procedures should be established and standardized.

Discussion on Q8

- Industry participants insisted that all the elements of Quality by design and risk management should be optional.
- The inclusion of Quality by design and risk management is however a prerequisite for improved flexibility for continuous improvement, post approval changes and any other regulatory relief.
- The CTD-Q describes the format of the submission. However similar to other ICH quality guidelines Q8 will describe the expected content.
- In particular industry expects from European regulators that the content of Q8 will not be used retrospectively for old products, especially in case of post-approval changes.
- P2 can be used to support a low risk classification of a product.
- Although P2 can support the preparation of an inspection, it cannot define the scope of the inspection. The scope is always defined by the inspectorate. There is a need for better understanding the different roles of inspectors, reviewers and sponsors. The role of the inspector is not to assess everything.
- Not all participants agreed that the use of P2 after approval is helpful. The fear is that too frequent up-dates are requested and that a possible benefit of P2 as a living document is jeopardized by excessive paperwork. A P2 document should not be mandatory for changes of old products.

- A participant mentioned that in the biotech industry the comparability protocols in the US have lead to simplified post approval changes. It was discussed that also for all other products the use of the P2 document could with the current post approval rules in the US be very useful. It is also expected that under the new legislation in Japan the P2 document will support a simplification of post-approval changes. The strong wish of industry is that also the European change procedures for variations should be adapted to allow more flexible approaches.
- It was agreed that good science would require reporting of failures that contributed to the understanding of the development and the decisions made during the development process.
- The regulators expressed that they do not expect more data than at present in P2 but knowledge about the product and processes.
- It was explained that for the most frequent post approval changes such as up scaling, equipment change and site change the experience from development could be used to support later similar post approval changes.

Pharmaceutical Affair Law Change and Quality Systems/Regulations in Japan

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Outline

- Pharmaceutical Affair Law (PAL) changes
  (A New system similar to US/EU)
- Quality Regulation changes under PAL
- Challenges and Opportunities

Revision of the Pharmaceutical Affairs Regulation (effective by mid 2005)

- ***Revision of the Approval and Licensing System***
  = From Manufacturing (or Importation)Approval/License to Marketing Authorization (From two sets to ONE)
- ***Enhancement of Post-marketing Measures***
  = To clarify the corporate responsibility of the safety measures as well as quality management

Revision of the Quality Regulation

- MAH's * responsibility for the quality management
- Drug Master File system to support CTD based application (eff. July 2003)
- Consolidation of the Legal Positioning of GMP
- Revision of GMP standards

* Marketing Approval Holder

■ *MAH's responsibility for the quality management*

- Supervise and manage the manufacturer and ensure the compliance of sites with GMP
- Ensure proper products release to the market
- Deal quickly with complaints and recall, etc.
- Conduct quality management based on post-marketing information etc.

■ *Consolidation of the Legal Positioning of GMP*

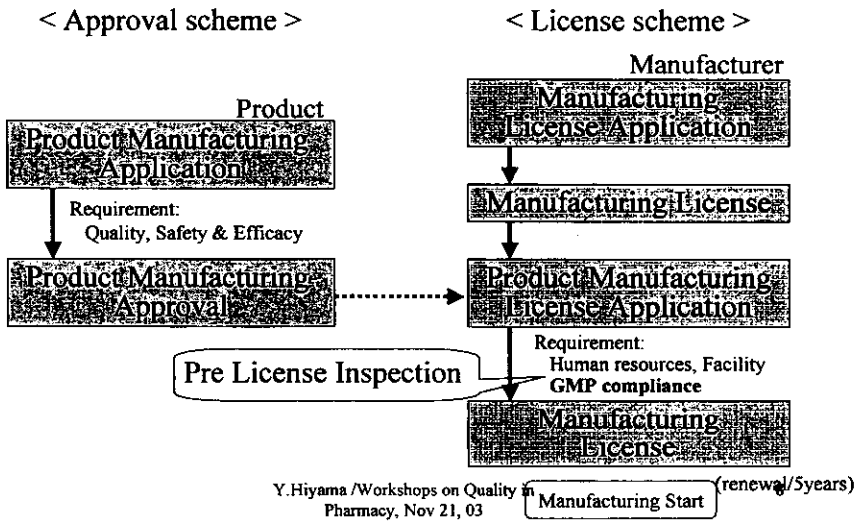
- Became a requirement for approval
- GMP inspection prior to approval and periodical GMP inspection in post-marketing phase
- GMP inspection at the time of application for partial change of the approval matters
- GMP inspection at foreign sites ONE regulation!

■ Drug Master File system to support CTD based application

- Common Technical Document based application became effective in July 2003
- Detailed Description on Formulation/Process Design And Manufacturing Process Controls
- Expand the scope of approval matters with rules for minor changes
- Need Master Files for API, (key intermediates, products)

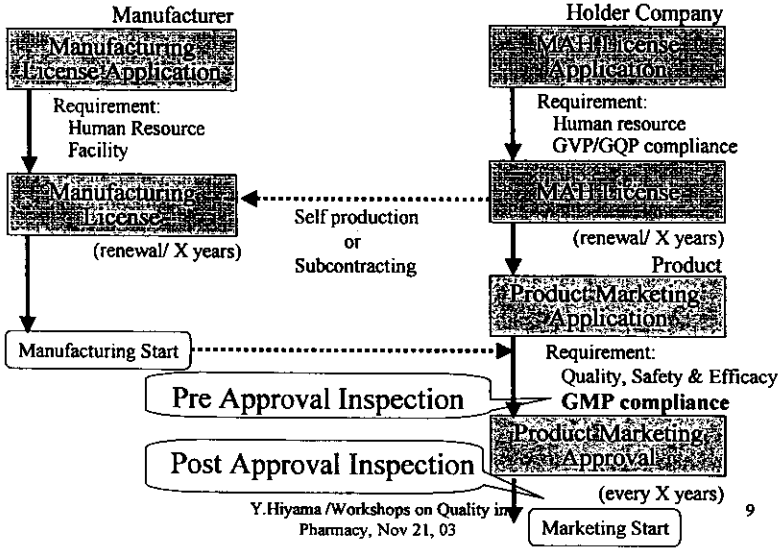
Flowchart of Approval and License

(current system /old system)



Flowchart of Approval and License

(revised system)



■ *Revision of GMP standards*

For Global Harmonization, including ;

- Strengthening of quality assurance function
- Introduction of change control requirement
- Utilization of electronic media, etc.
- Technology transfer(?)

Establishment of Incorporated Administrative Agency(SO-GO KIKO)

- Integration of review division, safety information management division and GMP inspection division
- Strengthening resources for review and inspection
- Establishment in April 2004

✧ Efficient review system
✧ More emphasis on pharmaceuticals with high risks

Expected Outcome

For Industry

- Establishment of quality management system from development to post-marketing

For regulatory authority

- Improvement of the approval review system by integration of the review and the GMP inspection
- To concentrate on higher risk products
- The establishment of effective, efficient, and streamlined quality regulation

System Development Activities by Health Science grant

GMP guideline (2002-2005)

Through Studies on GMP Quality Assurance supported by Health Sciences Grant (H14-Iyaku-04)

Inspection Policy/System(2003-2006)

Approval Matters and Minor Changes (2003-2006)

GMP Studies in 2002-2003

- (A) Quality systems *T.Nishihata (Santen Co)*
- (B) GMP regulations *Y. Koyama (Fujisawa Co)*
- (C) Tech transfer *K.Morikawa (NIHS)*
- (D) Lab control *S. Tadaki (Saitama Pref. Lab)*

Members:Industry (Pharma, Associated), Government (Prefecture Compliance, Prefecture Lab, NIHS , not central MHLW)

Work Principles: Bring Data/Experience not just Position/Opinion

From Quality systems (A)

Draft Proposal on introduction in "Ministerial Ordinance" or "Quality Assurance System Guide"

Quality assurance is defined that it ensures the quality, efficacy, and safety of marketing pharmaceutical products for human, and that it continuously provides medical institutions and patients the safety information including the proper use instruction based on the accumulated reports of adverse events.

Quality assurance of drug products is a company-wide, comprehensive concern as it covers manufacturing and quality controls of marketing drug products as well as the provision of information regarding post-release quality and proper use of drug products.

Pharmaceutical manufacturers/distributors should establish the quality assurance system, an integration of organization, responsibilities and authorities, procedures, processes and human/material resources that are necessary to achieve quality assurance. .....

The control items to be implemented in the quality assurance system are; "Declaration of responsibilities/authorities, organization, and resources (including risk assessment), " "regulations on document control, self-inspection and management audit,"manufacturing control, quality control," education/training," "validation," "the stability of post-marketing products," "change control," "non-conforming product," "complaint handling," "on recall/warning," "contract manufacturing," "post-marketing safety control," "annual report of the manufactured/distributed products (regulation on the stability of post-marketing products)."

Tech Transfer (C)

- Development report should be written and be transferred to manufacturer.
- Products specifications should be set by reflecting critical functional attributes. They should be clearly defined at the Product Quality Design stage. The Specs with Rationale should be in the development report, which should be available for review.

System Development Activities by Health Science grant-2

GMP guideline (2002-2005)

Through Studies on GMP Quality Assurance supported by Health Sciences Grant (H14-Iyaku-04)

Inspection Policy/System(2003-2006)

Approval Matters and Minor Changes (2003-2006)

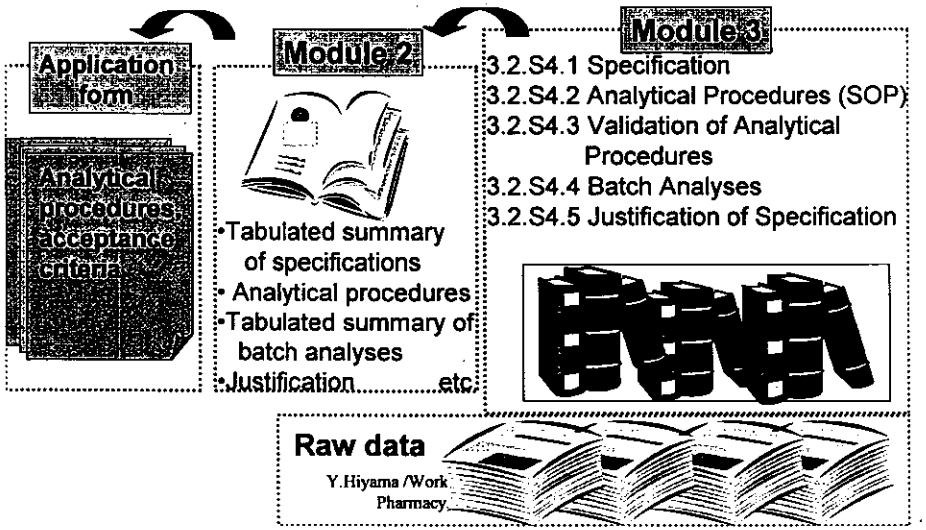
Problems with the OLD system

- Small range of the approval matters

Contained only spec lists with test methods

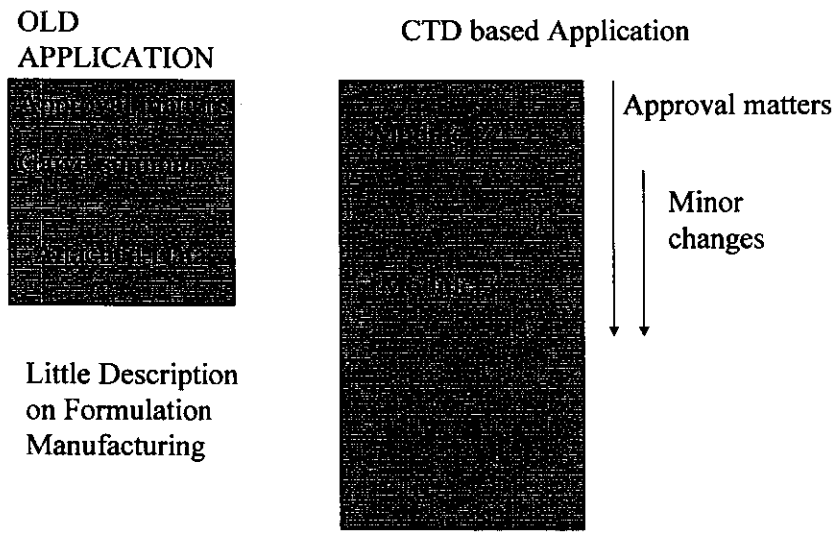
Manufacturing process design and controls had been ignored

Relationship between Application Form and CTD



Application Form Contains "Matters Subject to Approval"

- General name (for drug substance)
- Brand name
- Composition
- Dosage and administration
- Manufacturing process including control of materials-very limited description
- Indications
- Storage condition and shelf-life
- Specifications and analytical procedures



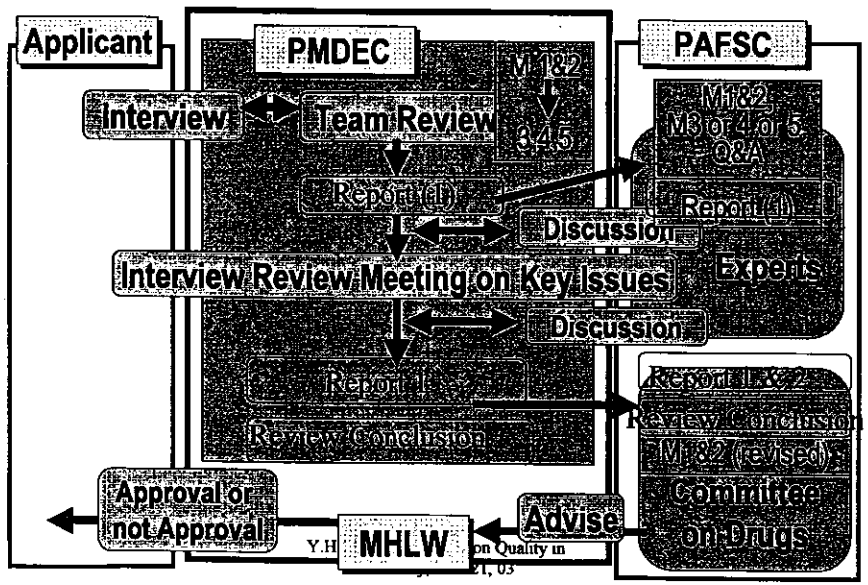
Opportunities by CTD application

- Complete description of product specific quality system
- Better knowledge transfer tool within the sponsor organization, between industry and regulator, and within the regulator organization

Role of Module 2 in Japan

- Module 2 bridges NDA Application Form and Module 3
- Module 2 is one of key review documents
  - Reviewers review Module 2 and then narrow down into Module 3 or 4 or 5 when they need more detailed information.
  - Module 1 and 2 together with review reports written by reviewers are evaluated in Pharmaceutical Affairs and Food Sanitation Council.

NDA Review Process in Japan



Challenges

- Training for reviewers and inspectors
  process/manufacturing sciences
- Industry's mind
  Reluctant or unable to give a complete story
  Regulatory personnel training
  Superficial development (meeting specs is all)

Module 1 in Japan

- Copy of **NDA Application Form**
- Certificates including statements by responsible persons for preparation of data and documents related to GLP and GCP
- Patent status information
- Research and development history of the product
- Conditions of use in foreign countries
- List of pharmaceuticals with similar pharmacological effect or indication
- Format of designation of poisonous/deleterious ingredients
- Draft Labeling
- Draft Protocol for Post-Marketing Surveillance

Characteristics of Japanese QOS

- Within CTD guideline
- Include plenty of figures and tables which summarize critical data
- Include narrative summary and/or discussion on data-integrated analysis
- Should be written in Japanese

The Mock-up of Japanese QOS

- Published by The Pharmaceutical Manufacturers' Association of Tokyo, Osaka Pharmaceutical Manufacturers Association and Japan Health Science Foundation.
- Merely shows an example of description for each section and just a reference for an applicant to prepare QOS.
- Not covers all information required for each NDA nor shows acceptance criteria for each categories.

PAT
The Concept

Real Time Process Monitoring & Control of the relevant stages of the tablet manufacturing process using NIR technology in order to provide:

- Improved process understanding
- Improved process control and feedback
- Enhanced assurance of finished product quality

⇨Platform for Real Time Release

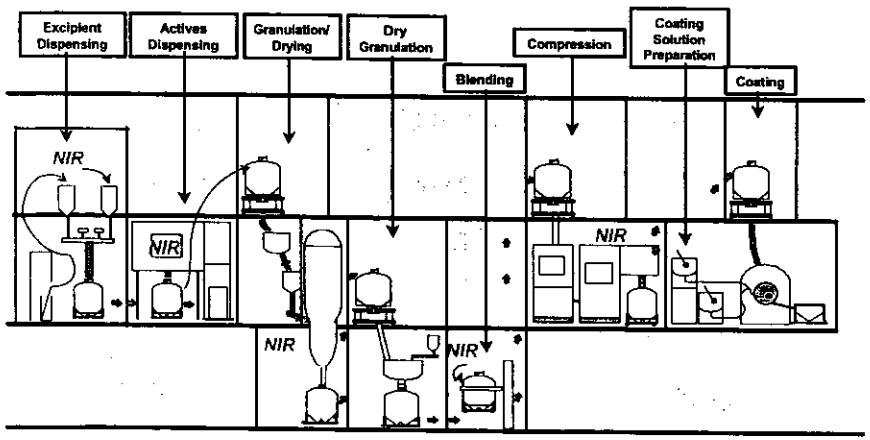
AstraZeneca

PAT
The Key Elements

- Identification & Monitoring of all incoming raw materials in warehouse & dispensaries
- Fluid Bed Drier end point control
- Continuous in-line monitoring and end point control of blending process
- On-line monitoring of Tablet Quality parameters against registered specifications
- Validated data management system

AstraZeneca

PAT
Process Scheme



AstraZeneca

PAT
Technical Solution

NIR-analysers for all applications:

- Dispensaries / FBD:
  multiplexed analyser using probes
- Blending:
  novel, purposed built analyser measuring through sapphire window in the IBC
- Compression:
  novel, purposed built analyser for non-destructive tablet measurement post tablet press prior to Erweka Tester
- Integrated IT-System covering all NIR applications
  (21 CFR Part 11 compliant)

AstraZeneca

Tablet Analyser

- Purpose-built analyser
  - Transmission (800-1300 nm) and,
  - Diffuse reflectance (1100-2300 nm)
- Non-destructive, real-time tablets analysis of tablets ex press prior to check weighing system

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Tablet Analyser Operation

- Sampling during the compression run
- Analyses each tablet for relevant quality parameters, including, amongst others:
  - Identity
  - Active Agent Content

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Background

- Established product
- Conventional immediate release solid oral dosage product
- Very robust conventional wet granulation process
- Commercial manufacturing experience of over 500 batches from same approved facility

Robustness of process demonstrated by 0 failures in > 500 Bx's

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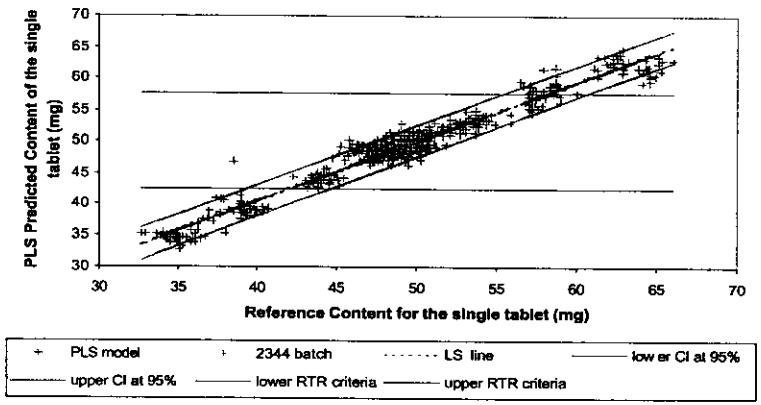
Understanding Process & PAT

A Calibration Example: Active Agent Content



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