Keynote

GMP & Validation – from disaster, via overkill, to common sense.

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Melbourne - July 2016

National GMP & Validation Forum

Hosted by PharmOut

My thoughts

- Power in the GMP world, leaders and followers.
- When validation became an industry.
- Risk based - Response to an increasingly complex world OR cop out?
    - GMP for 21st Century.
    - Risk based thinking.
    - Impact and criticality.
    - Risk assessment and management.

Power in the GMP world, leaders and followers

The world powers in GMP

- PIC/S – Pharmaceutical Inspection Cooperation Scheme (GMP follows EU GMP)
- WHO (Own GMP based on EU GMP)
- EMA and European Commission
- Japan PMDA (Pharmaceutical and Medical Devices Agency) (Following PIC/S and joining)
- US FDA (PIC/S member but has own GMP (CFR))
- Chinese SFDA (Following WHO and PIC/S)

The world powers in GMP – which order would you put them in??

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Why does US FDA have such a high profile?

- Protects the largest market for medicines.
- GMP core has always been (Federal) Law.
  - Failure to comply is a felony.
  - Individual accountability.
  - Requires specificity of non-compliance.
- Freedom of information largely responsible for the high profile:
  - Form 483s & warning letters published.
  - Sharing interpretation of the law and guidance increases penetration & strength!
  - Holds the inspectors to account publically = greater consistency (maybe!).

When validation became an industry, and then matured

Validation – essential, industry or sport?

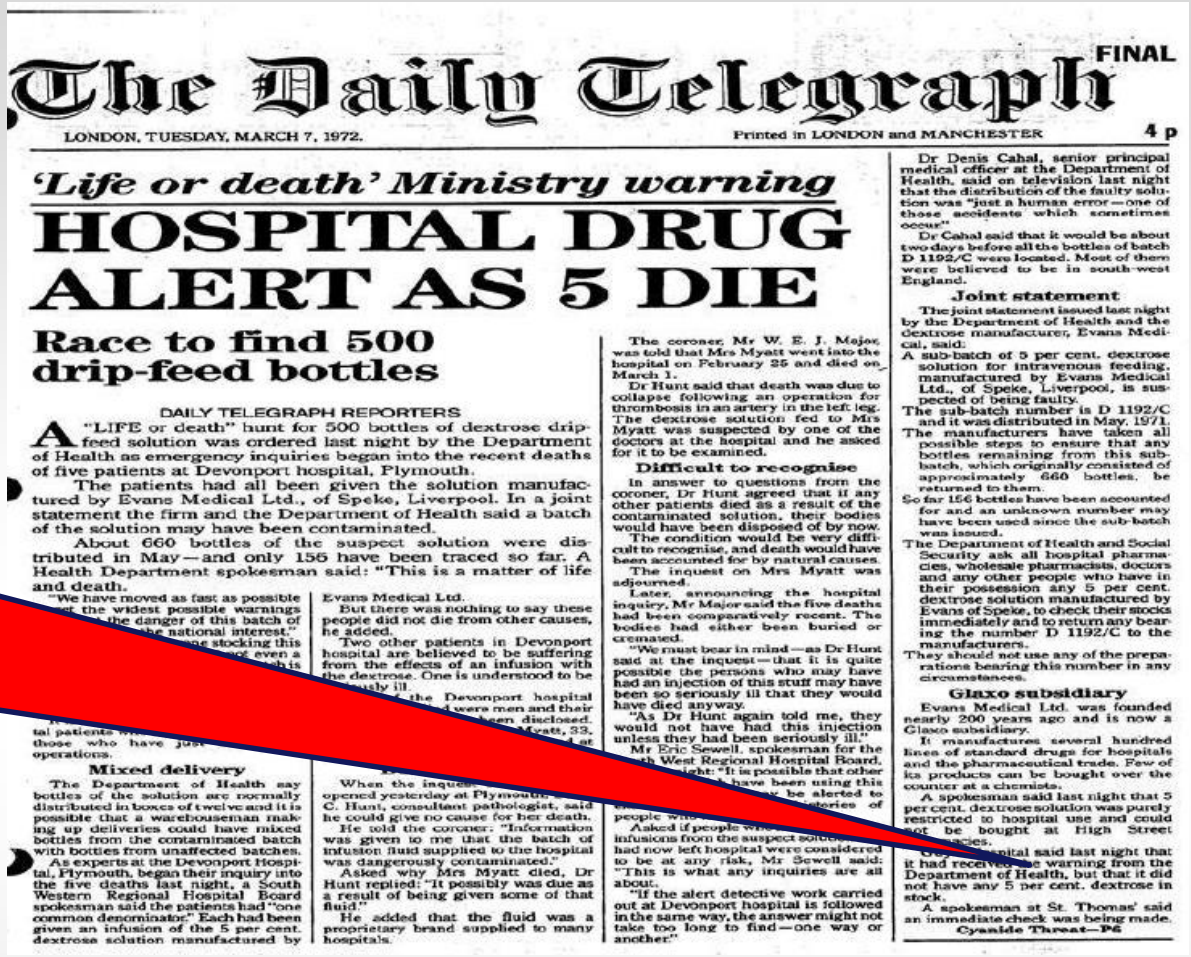
- Remember where it all began ????
  - Dead patients from non-sterile terminally sterilised LVPs.
  - Autoclave performance, cycle definition and cycle evidence.
- Like many regulatory initiatives (safety & quality), they emerge from a disaster.

The roots of validation as we know it!

- It all began in the 1971.
- From sterility disasters
  - 1971 - 7 deaths in USA.
  - 1972 (7th March, products manufactured in 1971) - 5 deaths at Devonport Hospital, UK.
- Originally sterilisation based.
- Then evolved into all Product, Process and Facility matters + even personnel.

Devonport

Root cause found at Evans Medical, part of Glaxo.



The Daily Telegraph FINAL

LONDON, TUESDAY, MARCH 7, 1972. Printed in LONDON and MANCHESTER 4 p

'Life or death' Ministry warning

HOSPITAL DRUG ALERT AS 5 DIE

Race to find 500 drip-feed bottles

DAILY TELEGRAPH REPORTERS

A "LIFE or death" hunt for 500 bottles of dextrose drip-feed solution was ordered last night by the Department of Health as emergency inquiries began into the recent deaths of five patients at Devonport hospital, Plymouth.

The patients had all been given the solution manufactured by Evans Medical Ltd., of Speke, Liverpool. In a joint statement the firm and the Department of Health said a batch of the solution may have been contaminated.

About 660 bottles of the suspect solution were distributed in May—and only 156 have been traced so far. A Health Department spokesman said: "This is a matter of life and death.

"We have moved as fast as possible ... the widest possible warnings ... the danger of this batch of ... the national interest."

... stocking this ... even a ... wish is ... those who have just ... operations.

Mixed delivery

The Department of Health say bottles of the solution are normally distributed in boxes of twelve and it is possible that a warehouseman making up deliveries could have mixed bottles from the contaminated batch with bottles from unaffected batches.

As experts at the Devonport Hospital, Plymouth, began their inquiry into the five deaths last night, a South Western Regional Hospital Board spokesman said the patients had "one common denominator." Each had been given an infusion of the 5 per cent. dextrose solution manufactured by Evans Medical Ltd.

But there was nothing to say these people did not die from other causes, he added.

Two other patients in Devonport hospital are believed to be suffering from the effects of an infusion with the dextrose. One is understood to be ... ously ill.

... the Devonport hospital ... were men and their ... been disclosed. ... Myatt, 33, ... at

When the inquest ... opened yesterday at Plymouth ... C. Hunt, consultant pathologist, said he could give no cause for her death.

He told the coroner: "Information was given to me that the batch of infusion fluid supplied to the hospital was dangerously contaminated."

Asked why Mrs Myatt died, Dr Hunt replied: "It possibly was due as a result of being given some of that fluid."

He added that the fluid was a proprietary brand supplied to many hospitals.

The coroner, Mr W. E. J. Major, was told that Mrs Myatt went into the hospital on February 25 and died on March 1.

Dr Hunt said that death was due to collapse following an operation for thrombosis in an artery in the left leg. The dextrose solution fed to Mrs Myatt was suspected by one of the doctors at the hospital and he asked for it to be examined.

Difficult to recognise

In answer to questions from the coroner, Dr Hunt agreed that if any other patients died as a result of the contaminated solution, their bodies would have been disposed of by now.

The condition would be very difficult to recognise, and death would have been accounted for by natural causes.

The inquest on Mrs Myatt was adjourned.

Later, announcing the hospital inquiry, Mr Major said the five deaths had been comparatively recent. The bodies had either been buried or cremated.

"We must bear in mind—as Dr Hunt said at the inquest—that it is quite possible the persons who may have had an injection of this stuff may have been so seriously ill that they would have died anyway.

"As Dr Hunt again told me, they would not have had this injection unless they had been seriously ill."

Mr Eric Sewell, spokesman for the ... th West Regional Hospital Board, ... ight: "It is possible that other ... have been using this ... be alerted to ... stories of ... people who ...

Asked if people who ... infusions from the suspect ... had now left hospital were considered to be at any risk, Mr Sewell said: "This is what any inquiries are all about.

"If the alert detective work carried out at Devonport hospital is followed in the same way, the answer might not take too long to find—one way or another."

Dr Denis Cahal, senior principal medical officer at the Department of Health, said on television last night that the distribution of the faulty solution was "just a human error—one of those accidents which sometimes occur."

Dr Cahal said that it would be about two days before all the bottles of batch D 1192/C were located. Most of them were believed to be in south-west England.

Joint statement

The joint statement issued last night by the Department of Health and the dextrose manufacturer, Evans Medical, said:

A sub-batch of 5 per cent. dextrose solution for intravenous feeding, manufactured by Evans Medical Ltd., of Speke, Liverpool, is suspected of being faulty.

The sub-batch number is D 1192/C and it was distributed in May, 1971.

The manufacturers have taken all possible steps to ensure that any bottles remaining from this sub-batch, which originally consisted of approximately 660 bottles, be returned to them.

So far 156 bottles have been accounted for and an unknown number may have been used since the sub-batch was issued.

The Department of Health and Social Security ask all hospital pharmacies, wholesale pharmacists, doctors and any other people who have in their possession any 5 per cent. dextrose solution manufactured by Evans of Speke, to check their stocks immediately and to return any bearing the number D 1192/C to the manufacturers.

They should not use any of the preparations bearing this number in any circumstances.

Glaxo subsidiary

Evans Medical Ltd. was founded nearly 200 years ago and is now a Glaxo subsidiary.

It manufactures several hundred lines of standard drugs for hospitals and the pharmaceutical trade. Few of its products can be bought over the counter at a chemists.

A spokesman said last night that 5 per cent. dextrose solution was purely restricted to hospital use and could not be bought at High Street ... ces.

... spital said last night that it had received ... e warning from the Department of Health, but that it did not have any 5 per cent. dextrose in stock.

A spokesman at St. Thomas' said an immediate check was being made.

Cyanide Threat—P6

"The (Clothier) committee considers that too many people believe that sterilisation of fluids is easily achieved with simple plant operated by men of little skill under minimum supervision, a view of the task which is wrong in every respect."

Hazard and operability study (HAZOP)

- Emerged from the ICI Company in 1977, after the Flixborough UK disaster.
- Primary key words
  - Flow; Temperature; Pressure Level; Separate (settle, filter, centrifuge);

Risk based – Cop out?

GMPs and guidance became more and more prescriptive from 1971 to 2000

- Sterilisation understanding
  - NCGs; dryness, superheat, 6log reduction of resistant spores.
  - Load definition; cycle development.
  - Process cycle evidence.
  - Qualification & Validation concepts developed.
- Validation becomes a profession:
  - VMP; IQ; OQ; PQ; PV.
  - Validation departments.
  - Outsourcing to experts and horsepower.

Then Y2K hit us!

- Fear of catastrophic loss of control and information.
- Really consolidated the importance of IT system integrity.
  - Helped strengthen 'Computer Systems Validation' as a discipline.
  - Whole departments formed.
  - Thousands of experts emerge.

We survived Y2K mostly intact – then what next?

- Early 2000's, industry started to challenge the value of all the effort. Was it well directed?
- Regulatory response, lead by US FDA was:
  - GMPs for the 21st Century.
  - Risk based GMP.
  - Not our (US FDA) problem, it was industry that got carried away!

The solution was - Risk based thinking ???????

- We developed a whole raft of concepts:
  - Systems based approach (management & technical).
  - Impact (Direct, Indirect, No).
  - Use of structured and documented risk assessments.
    - FMEA becomes the favourite.
    - Severity, Frequency of occurrence, Ease of detection of adverse events.

Consistent focus

- Sterile products
  - PNSU
  - Personnel primary contamination source
  - Aseptic processing dominates;
  - very few issues around terminal sterilization (we must have cracked that one!)
- BUT then……
  - Rise of biologics and increasingly complex products, presentations, and manufacturing operations.

What was/is Risk based thinking ???????

- Do we really mean risk based?
- When was the last time you ntified and accepted/rejected e percentage of pati .
- Actually its no , its about prioritising our effort actually affect the "critical qualit of the product.
- - Yes/No; In/Out; Critical/Non-mpact/No-impact.

doubt, it goes into the IN bucket.

In some jurisdictions the Risk Assessment process has become the requirement, more important than the output!

2010 - We realised we swallow pills, not great mounds of paper (GMP)

- So we decided to get much smarter:
  - Cost reduction and efficiency is OK language for GMPers.
  - Product and process understanding. What really affects/ensures appropriate & consistent product quality.
    - CQAs and CPPs.
    - Product & Process 'Life cycle'
  - Technology comes to the rescue (at last??)
    - Reawakening of parametric release.
    - PAT
    - Real-time release (RTRT).
  - Verification:
    - Experts (SME).
    - On-going; Continuous & Continued.

Our thinking continues to mature →2015 – Cross-contamination

New thinking driven by industry trends

- More potent & toxic products.
- Demise of the block-buster product:
  - Big bang facility, something in the past.
  - Adaptable manufacturing units.
  - Avoid too many dedicated facilities on a whim!
  - Personalized medicines.
- Time to market comes into focus:
  - Shortens project lead times.

X-contamination control initiatives

- ISPE RiskMaPP.
- EU & PIC/S GMPs Ch 3 & 5 revision
  - Risk based on ADI/ADE (allowable daily intake).
  - Science and toxicology rules OK
  - Complex principles; a challenge for low margin generic world.
  - Rise of the toxicologist into the GMP world.
- Now we move into the phase of streamlining and rationalisation of the initiatives.
  - Screen product and processes.
  - Focus on the tricky critical stuff.

Then back to some basics →2015/16 – Integrity

Integrity & Accountability

- Data integrity (hot topic 2015 & 6)
  - Technical
    - Records
    - IT systems
  - Cultural
    - Doctoring records.
- Counterfeiting
  - Fraudulent products.
  - Facilities.
- Virtual businesses
  - Challenge of multiple manufacturing sites
  - Virtual Locum QP/Authorised person

And finally
What next ??????

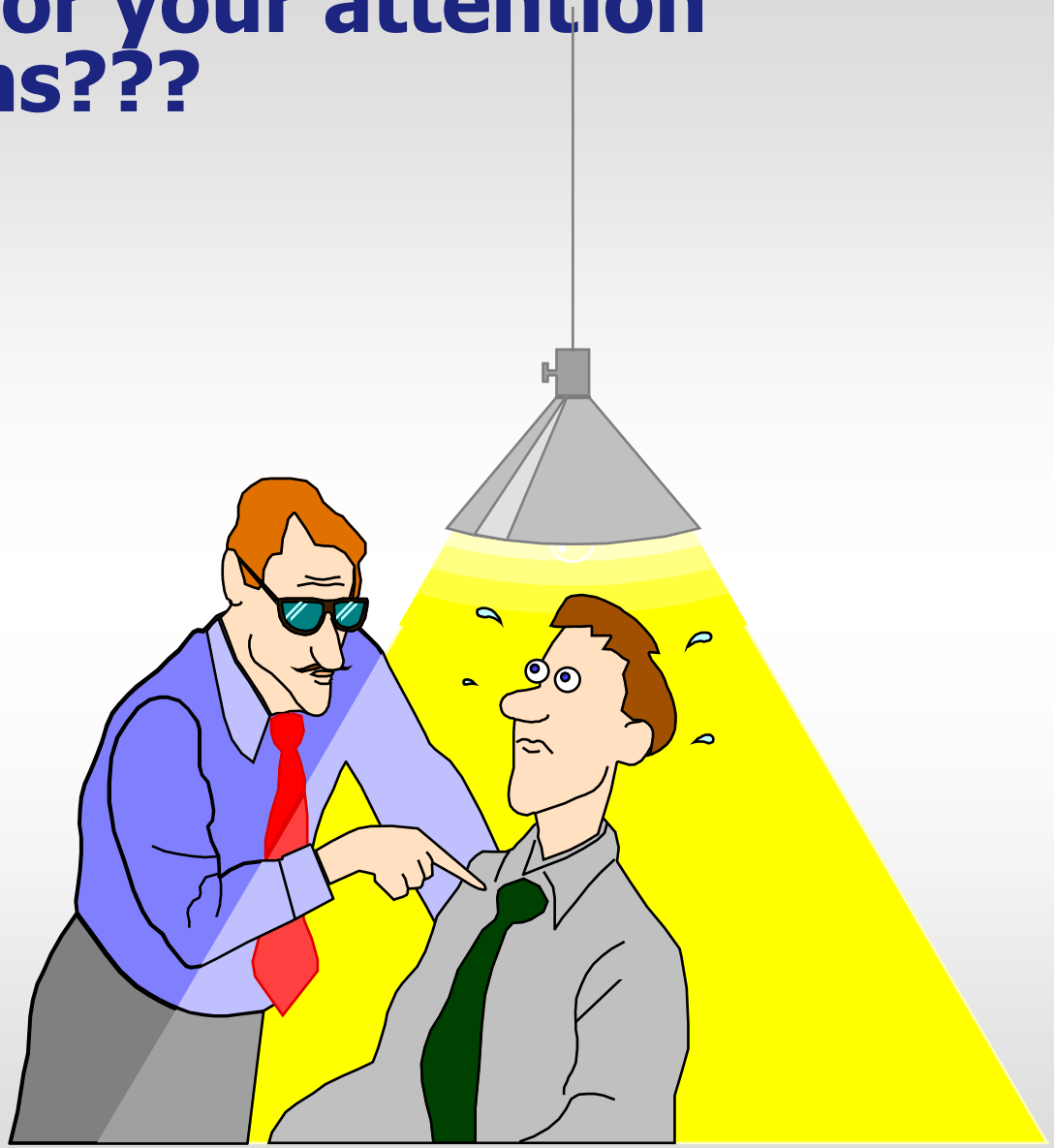
What next ?

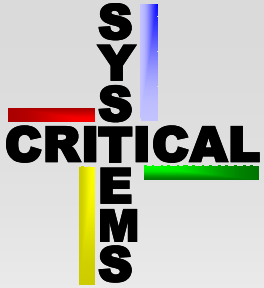
- Exploiting and maintaining technology.
  - The fitness for purpose of the engineering team.
    - Knowledge; Employment; Responsibility; Reward.
  - Performance and reliability of systems:
    - Efficiency.
    - Availability = Uptime. Mean time between failures.
    - Vendor dependence & assurance.
  - Upgrading and improvement.
    - Exploit proven available technology.
    - Don’t let assets get out of date.

What next ?

- Production engineering:
  - Next stage from QbD.
  - Design with production efficiency and robustness in mind.
  - Machine reliability.
- New or rediscovered technologies:
  - In the world of isolators and closed RABS, the challenges of fragile hydrogen peroxide vapour (HPV) continue – fragile process, lengthy to qualify and validate effective cycles.
  - Now ClO_2 and NO_2 systems are being developed and promoted.
  - One NO_2 system, called 'Noxiliser' has just received US FDA 510k clearance for medical device sterilisation.
- Exploitation of rapid and instantaneous micro methods.

Thanks for your attention
Questions???





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