Validation deaths across america. it was as a

Business, Industries

Validationin the Pharmaceutical IndustryIntroductionThe Manufacture of pharmaceuticalproducts is a highly complex procedure and is one of the most regulated sectorsof any manufacturing industry. The original method of pestle and mortarof the past has have given way to highly advance and complex manufacturingprocedures of pharmaceutical products. What was once the domain of chemist orpharmacist are now controlled by computerised system.

Due to the growth of thepharmaceutical sector, fuelled by the demand for existing and new products, themethods of ensuring that all products that are released to the markets are safe, pure and effective for use by the general public have also developed. Theregulatory requirement of the sector by such agencies as the FDA (USA), EMA(EU), MHRA (UK) and the HPRA (Ireland) have helped to ensure the high standardsof quality and so preventing the mistakes of the past. BackgroundThe history of RegulatoryRequirement in the Pharmaceutical Industry is a history of tragedy.

At thebeginning of the nineteenth century there was very little if any Regulatoryrequirement for the manufacture of medical products. Company would advertisetheir latest products some of which would contain many dangerous substances. Theseproducts were sold as a cure-all`s for many different diseases and illnesses, and some were regularly given to children asin the case of opium based produces to help with teething. As a result of the tragedieFJ1 s it became clear that apath forward required to control the manufacture of Pharmaceutical productsthrough GMP using strong regulations and procedures. After eachtragedy stronger regulation was introduced to ensure FJ2 such mistakes may notre-occuragainFJ3 . The

FJ4 pure Food and Drug Actand the Meat Inspection Act which were both signed into law on June 30th1906. This is widely accepted as the founding date of what is now the FDA. The ElixirSulfanilamide Disaster in the USA in 1937.

Between the months of September and October 1937 Elixir Sulfanilamide was responsible for more than 75 deaths across America. It was as a result of poor understanding of the chemicals used, and poorregulatory requirement for the testing of products before been released on tothe market. The company Massergill and Co discovereda method to dissolve Elixir Sulfanilamide using aformula containing diethylene glycol (antifreeze) and raspberry flavoured water, this give it a nice appearance and a sweet taste which would make it appealingto children. The new formula was sent to production and a week later releasedon to the market. Within week there were reported cases of deaths due to theproduct. As a consequence of theSulfanilamideDisaster the federal government realised that greater regulation were required, this lead to the Food, Drug and Cosmetic act of 1938. Up to this point a companyFJ5 could not be prosecutedas was the case of Massergill and Co who were only charged with mislabelling ofthe product.

With the introduction the Food, Drug and Cosmetic act (FDCA) companies were required to carry out safetytesting on their products and would be held accountable for deaths or injurycaused by their products. The goal of the Food, Drug and Cosmetic act was toverify that the food, drugs and cosmetics were pure, safe and effective beforebeen released for sale. The FDCA also

ensure that the correct labelling andpackaging was used. The Sulfathiazole tragedy occurredas a result of the Winthrop Chemical Company of NewYork released sulfathiazole tablets which were contaminated with phenobarbitalto the marketFJ6 , the resultwas hundreds of deaths and injuries. The FDA`s investigation revealed seriousplant control deficiencies and irregularities in the firm’s product recallprocesses. As a result of the Sulfathiazoletragedy the FDA revise their currentrules on manufacturing and quality controls.

The 1941sulfathiazole disaster was hailed as the birth of good manufacturing practices(GMP). Future amendments tothe FDC 1938 act were due to the Thalidomide Tragedy between 1953-1962 Thalidomide was developed as a sleeping aid and given to workers by Chemie Grunenthal , one workedgive it to his pregnant wife resulting in their child been born without ears. The drug was sold in over 40 different countries. In the USA FDA officerFrances Kelsey prevented the drug from been approved and resulted in preventthe same tragedy happening in the USA. She was awarded President’sAward for Distinguished Federal Civilian Service fromPresident John F. Kennedy.

GMPGood Manufacturing Practices Priorto FJ7 1970 the quality andsterility of products was only completeFJ8 at final producttesting. The Septicaemia outbreak of the early 1970`s in hospitals which wascaused Enterobacter cloacae of E. agglomerans due to improper sterilising of large volume parenteralresulting in 54 deaths. As a result of the FDA investigation which resulted intotal product recall and closure of the plant. The FDA proposed changes to theGMP`s which resulted in the introduction of GMP`s procedures

In 1976 the Medical Device Amendments wassigned in to law. Thisgive FJ9 the FDA greater powersover the manufacture of medical products.

The FDA also Proposed changes to theGMP`s with a strong FJ10 emphasison the Sterilisation procedures used to sterilize manufactured products. It wasat this time that terms validation and Qualification began to be used withinthe pharmaceutical sector. In 1978 the cGMP`s rules final established theminimum current good manufacturing practices for the manufacturing process , packing , storage and transportation of medical products and devices.

In 1979 Good Laboratory practicesGLPs was established. In 1980 the Infant formula Act waspassed into law due to the serious illness of dozens of children due to thelack of chloride in soy based formula. The Act give greater power to the FDA toenforce a minimum nutritional quality standard. In 1983 the Anti-Tampering act wasintroduced making it a crime to tamper with medical packing, this was a result oftampering and lacing with cyanide of Acetaminophen capsulescontainers. Also in 1983 better documentation was published to inspectcomputerised systems in drug manufacturing which was the beginning in computervalidation.

The Therac Tragedy wasanother step along the road of GMP which was a result of software errors. Many valuablelessons were learned and better quality practice ware implemented to improvethe quality and testing of the software used in medical devices. In 2001 the EuropeanUnion (EU) published a set regulation called Eudralex.

Eudralex are a set ofregulations that govern the manufacture of medical products for both human andveterinary use. Eudralex consist of 10 volumes, volume 4 deals with GMP`s has19 Annex. Annex 15 deals with Qualification and Validation. Annex described themethod of qualification and validation of the facilities, utilities, equipment(FUE) and the process used to manufacture the medical product. It is now the responability of the manufacture tocontrol the critical aspects of theproduce life cycle. Any changes in the product, process or FUE should bedocumented and assessed for its impact on the processes.

In 2015 an updatedrevision of Annex was published to take into account the changes in othersectors of the EUDRALEX. Along the long andtragic road that has led to the current point where the Pharmaceutical Industryis now one of the most regulated industries where GMP is something that isbuilt into every stage of the planning and manufacturing and wherequalification and validation are a critical part of every stage of the fulllife cycle of every product. GMP regulatory is now a legal requirement forevery company wishing to manufacture medical products. ValidationQuality is very important in themanufacture of any produce sold today. But when that productFJ11 is a lifesaving products like Pharmaceutical products, quality becomes evenmore important. Quality is now a mandatory requirement by both Governments andRegulatory bodies.

CGMP requires that quality be built in to the product atevery stage of its life-cycle. Validationis a documented procedure to provide assurance that a process reaches aspecified level of quality attributes consistently and be

able to reproducethat consistently during all the different stages of the life of the product. Process Validation is a process tocollect data throughout the life-cycle of a product which provides scientificevidence that the process is capable of producing consistent high qualityproduct to ensure that it meets the regulation guideline requirements of suchregulatory agencies like the FDA and EMA. In the case of equipment validationit is referred to a Qualification. Inshort you validate a process but you qualify equipment. There are 4different types of validation.

Prospective Validation ProspectiveValidation is validation done before distribution of a new process or anexisting process that may have had some changes made to it. The requirementsfor Prospective Validation is to provide documentary evidence that the processworks in accordance with the pre-prepared protocol and is normally completedbefore the product is released for sale and all the validation protocols areexecuted before the process is ready for commercial use. At the productdevelopment stage the process is broken down into its own individual stepFJ12 s and each step is checked for its criticality tothe quality of the product. All the facilities, utilities, equipment (FUE) as wellas the test methods must be fully validated. The Master batch documents canonly be prepared after all of the critical parts of the process have beendetermined. This method of validation is the preferred approach and is the mostwidely used method of validationConcurrentValidationConcurrent validation is validationthat used documentary evidence to show that a process or FUE preformed the wayit is expected to, based on information gathered during the actual productionprocess. This method measured all the critical steps within the

process and endtesting and compared them to existing data to ensure the process is preformingas expected within the existing control parameters.

An example of whereConcurrent Validation was used is during the Ebola disease outbreak wherevalidation is being done while the product is being manufactured. It is notusually allowed except in one off cases or as in the Ebola example where it isurgently required. Retrospective Validation RetrospectiveValidation is a validation carried out on a well-established process usinghistorical documentary evidence to show that the process dose what it is meantto do and to the level expected of it. Retrospective Validation is only used onwell-established process where there has been no change to the raw material, FUE or the production process which are critical to the quality of the product. Retrospective Validation should only be used where there is enough historicaldata to show that the process has being consistently producing produce thatmeet pre-established quality parameters. During the retrospectivevalidation samples, should be taken from all batches made during the validationperiod includingbatches FJ13 that have failed, the number ofbatches should be a large enough to show consistency of the process. Revalidation Revalidationis used when there has been a change to any part of the process and FUE, it isused to determine the effect of the change on the process and FUE and decide ifrevalidation is required. An example of revalidation is if a piece of equipment moving FJ14 for one location to another, revalidationwould be carried out to ensure that the equipment’s acceptance criteria is met.

Another examplewould be where maintenance work carried out and key components were changed, Revalidationwould be required before the equipment is returned to production. Differentstages of ValidationUser requirement specification (URS) The URS isa document that described the requirements specification of a new process asrequired by the owner or end user. User Requirements Specifications are written by thesystem owner or end user typically before the validation process starts. The UserRequirements Specifications document is not intended to be a technical documentbut more a general description of the requirements of the intended process andshould be used as a reference throughout the validation life cycle. Validationcan be broken down to several different stages which are called Qualificationsstages.

Design Qualification (DQ) Installation Qualification(IQ)Operational Qualification (OQ)Performance Qualification (PQ) Design Qualification(DQ) It providesevidence that the URS requirements have been met through FS/DS and any riskshave been mitigated through FMEADQ is the design of theinstrument it is not evidence of the URS being met, it is used to state the URSand the FS/DS and will show how the user requirements will be tested. Inclusionin the DQ also ensures that any failure modes are identified and will also becontrolled in either the IQ/OQ of in an OP/procedure. InstallationQualification (IQ) Installation Qualification (IQ) provides documentary proof that theequipment or system has been delivered and installed in accordance with theinstallation specification and that the respective DS has been tested to ensureURS are met. The utilise such as water, air and electric would be verified atthis

stage. OperationalQualification (OQ) Operational Qualification provides documentary evidence that the FacilitiesUtilities, Equipment (FUE) and processed can consistency perform to the standard stated in theoperational specifications. Testthat may be completed at this stage include and functional testing of theequipment Performance Qualification (PQ)FJ15 PerformanceQualification provides verification that the process can constantly produce aquality product over a certain period.

PQ is preformed when there are no down-streamchecks. Benefits of Validation In the previous section, we have looked at theevolution of regulatory requirements leading to GMP for the production ofmedical products and how validation became a very important tool in thisprocess. We have also looked at the different types of validation and thedifferent qualification stages within validation Validationis a regulatory requirement but that is not the only reason that companypreform validation.

There are a lot of benefits of validation some of them arelisted below. leading tolower rejectionReductionin production and quality cost. Increasedquality. Reductionin lost time. Reductionin the failure rate. Increasedthe manufacturing capability by reducing failures and rework.

Requiredless in-process and end-of-line testing. Can be usedto investigate invalids or deviation during production. Variationfrom batch to batch is minimized. Bettercompliance with all regulatory agenciesGetting themost from the process and equipment. Betterscheduling of equipment maintenance. Improvesthe training of production staff which gives them a

better understanding of theproduction processesConclusionThe Pharmaceuticalsector is now one of the most regulated industries and safest. People haveconfidence that product`s or device are safe to use and will not have any majorside effects.

Regulatory guidelines provides a clearpathway for the manufacture of medical products. Validation is a key tool inproviding the quality assurance that is required to manufacture medicalproducts.