CASE HISTORY: FAILURES IN CGMP COMPLIANCE

Mr. R.M. Gupta (M. Pharm.), is a free lancer consultant for US DMF, COS, ANDA, ACTD, CTD, eCTD and other regulatory submissions. guptarmg1952@gmail.com

He is associated with Perfect Pharmaceutical Consultants Pvt. Limited and Global Institute of Regulatory affairs (Pune, India)

The readers are invited to post their queries at guptarmg1952@gmail.com

Introduction:

GMP is a very delicate issue. It looks simple but it is very difficult to practice successfully. Every body knows rules of GMP but very few are successful in interpreting the same precisely.
GMP is a system to avoid errors through systematic functions.
GMP does need ample of money as good things do not come free or cheap.
Further, it also requires high degree of scientific knowledge, skill and expertise.
GMP projects are difficult and challenging. However, at the same time they are rewarding and interesting. You must achieve GMP for your company.

Followings are the eight most common mistakes resulting in failures in cGMP Compliance:

1	Mistake:1	Failure to Employ properly qualified, experienced and trained people
2	Mistake:2	Failure to Maintain adequate funds for GMP infrastructure
3	Mistake:3	Failure to Devote sufficient time to manage GMP
4	Mistake:4	Failure to Solicit support from consultants and regulatory bodies.
5	Mistake:5	Failure to Maintain constant vigilance on GMP
6	Mistake:6	Missing Useful associations
7	Mistake:7	Failure in Time Management
8	Mistake:8	Failure in Designing and Maintenance of facilities

MISTAKE: 1
FAILURE TO EMPLOY PROPERLY QUALIFIED, EXPERIENCED AND TRAINED PEOPLE

CGMP compliance requires that the key people shall be appropriately qualified and experienced with respect to the products manufactured at the site.
Ensure that the people have:

1	Appropriate Qualification and at least 3-4 years experience in required product line.
2	High relevancy of the experience with job profile.
3	High IQ and Vigilance for cGMP.
4	Basic understanding of the scientific principles involved in GMP

Followings are few Case Histories of erroneous appointments of key personnel

Case History 1: Failure to appoint proper candidate as QC In charge

Company	Bulk Drug unit at Nashik
Candidate	Doctorate in Biochemistry .No apparent experience and knowledge of Pharmaceuticals. No much awareness on method validation, impurity profiling and HPLC operations.
Appointment as	QC In charge
Problem Encountered	The person was effective in conducting day today analysis. However, he miserably failed in resolving complaints regarding stability, forced degradation and bioburden. He could not achieve standardization of the products with alternative methods. He failed in organizing drug master files.

Case History2:

Company	Reputed Pvt. Ltd. company in UP
Candidate	M.Sc., Lead auditor for ISO 9000 compliance
Appointment as	QC / QA In charge
Problem Encountered	No problem in day today QC work. However, he could not match documentation with cGMP Norms and the company failed repeatedly and bitterly during cGMP audits

Case History 3:

Company	Bulk Drug Unit in Mumbai
Candidate	B.Com 10 Years experience in Banking (Female)
Appointment as	Director Technical Operations
Problem Encountered	The lady was very dynamic. She upgraded the plant in consultation with experts in GMP. However, she failed in total GMP compliance. She had no adequate knowledge of pest control, bioburden, documentation and method validation. The GMP experts had guided her in this area but she was unable to understand the underneath objective and could not perform well

Case History 4:

Company	Manufacturing new drug formulations at remote site
Candidates	M. Pharm. (15 Years experience) appointed as Production Manager. B. Com (30 years experience) appointed as Project In charge
Problem Encountered	All the GMP proposed by M Pharm. was rejected by Project Manager. All previously appointed GMP consultants were fired and denominated. The company failed bitterly during WHO audit

Case History 5:

.

Company	Manufacturing pharmaceutical enzymes from Plant Exudates
Candidate	B.Sc. with 10 Years experience
Appointment as	Production Manager
Problem Encountered	Continuous strong complaints on heavy fungal contamination in finished products

Case History 6:

Company	Excipients Manufacturing Company
Candidate	IAS Officer (40 Years of experience)
Appointment as	Managing Director
Problem Encountered	MD has no knowledge of Pharma Industry. He considered Purchasing even USP/BP raw materials as waste of money. He commanded GMP at gunpoint without any formal training and support from Consultants. He could not run the company an inch towards GMP compliance over 5 years

MISTAKE 2: FAILURE TO MAINTAIN ADEQUATE FUNDS FOR GMP INFRASTRUCTURE

Funds are vital part of cGMP compliance. No money no GMP.

No.	The most common errors in managing funds for GMP are:
1	No well defined budget
2	Erratic release of funds for GMP
3	Anger, grief and nervousness on GMP expenses.
4	Continuous downward revision of GMP budget

Inadequate funds for GMP lead to:

1	Use of lower quality materials
2	Poor maintenance of machines
3	Poor vigilance

Followings are few Case History of failure in cGMP Compliance due to failure in management of funds for cGMP

Case History 1: No funds for buying current edition of Pharmacopoeias

Company	A Pharmaceutical Company in Delhi
Incident	Once (in year 2009) I was auditing a company in India. The company was in manufacturing Excipients as per IP/BP/USP standards. When I asked for the current official copies of products being manufactured at the site, just few relevant pages from pharmacopoeias were presented. I was shocked to see that the pages were from 2002 edition of BP/USP. They were not current to 2009 editions of BP /USP
Root cause	The company had no budgets to purchase official copies of Pharmacopoeias.

Case History 2: No budget for buying Primary Reference Standard

Company	Company at Jalgaon
Incident	No trace of Primary and Secondary References standards
Root cause	MD explained the situation as per follows “We are manufacturing 50 products and we have no budget to procure official reference standard for each product Reference standard are difficult to source and are also very expensive .One single standard may cost Rs. 20,000=00 to 30,000=00.

Case History 3: No budget to appoint QA manager

Company	Company at New Delhi
Incident	No QA Staff. No QC Staff. The owner himself performs both the functions
Root Cause	The owner explained "A well qualified & experienced QA Manager Costs 6.00 – 10.00 lakh per annum. I do not have good profits in the business. Hence I am avoiding such expenses. "

Case History 4: No budget for installing HVAC system

Company	**Company near Mumbai (Anticancer bulk Products)**
Incident	No HVAC system at site
Root Cause	Proprietor Explained "I know that an efficient HVAC system is the must to comply with GMP. However, my profits do not permit me to install such a expensive system "

Case History 5: No budget to modernize Water System:

No.	**Company in Karnataka**
Incident	No Proper Water system installed at the site.
Root Cause	GMP requires proper design, operation and maintenance of water system. However, due to inadequate budget the water system was never designed, resin beds were never reactivated; RO membranes were never cleaned and sanitized.

Case History 6: No budget for Prevention of Water Pollution

1	Inadequacy of GMP funds never permit any spending on water pollution treatment.
2	I observed stagnant pools of water and drains over flowing.

Case History 7: No budget for calibration and validation activities

No.	**Many observations during my audits**
1	The management always supports calibration and validation. However no money is released for the activity.

Case History 8: No budget for Housekeeping and maintenance

No.	**Many observations during audits**
1	GMP requires regular painting of walls, ceiling, polishing of floorings, buffing of machine contact parts.
2	In GMP budget this activity is given last priority and practically no money is spent.

MISTAKE 3: LACK OF KNOWLEDGE & VIGILANCE

GMP is very delicate affair. It is constantly changing. It is difficult to interpret and implement. It is different for different products. It is perceived differently by different regulatory authorities.
It demands safety and efficacy of the products till it is consumed by the patient.
It certainly needs continuous monitoring. Key people must update themselves with local and global regulations from time to time.
Normally, following are the root causes of poor GMP knowledge.

1.	Never organizing /attending GMP seminars, conferences, meets and workshop.
2.	Never checking regulatory websites for GMP updates
3.	Never performing self audits
4.	Never subscribing for the latest technical publications on GMP
5.	Never Liaoning with FDA and competent authorities for their view on cGMP

Following are the Case History.

Case History 1: No trace of on GMP Literature

1	Company	Excipients Manufacturing Company
2	Vigilance	Absolutely No literature/posters/books on GMP No self audit
3	GMP Status	Very poor

Case History 2: No trace on GMP Literature

1	Company	Bulk Drug Unit
2	Vigilance	No GMP Literature No Interest facilities to check latest regulations No official copies of Drug Rules/Regulations No cGMP Training Materials
3	GMP Status	Very poor

Case History 3:

1	Company	Bulk Drug Unit
2	Vigilance	No Vigilance on activities going at site during odd Hours.
3	GMP Status	Very poor

MISTAKE 4: FAILURE TO SOLICIT SUPPORT FROM CONSULTANTS AND REGULATORY BODIES

Every organization needs external support for cGMP some or other time. External support is like insurance to meet difficult situations in GMP Compliance

Advantage of Technical Support

1.	Expert advice within minutes
2.	Quick resolution of problem
3.	Guaranteed success

Followings are few Case History of failure in soliciting support from Regulatory consultants:

Case History 1: No External support for designing SOP

1	Company	US FDA approved formulation unit
2	Incident	Unscheduled FDA visit
3	Task	Documentation to be updated
4	Problem	Key person for documentation was on leave and No external support was available for the same.
5	Result	Audit failed

Case History 2: No External Support for updating Quality Manual and SMF

1	Company	WHO Approved unit in Mumbai
2	Incident	Huge orders for few of the products under exhibition in a trade show
3	Task:	To provide DMF within a short time
4	Problem	Lack of experience is designing DMF. Further no regulatory consultant was ready to undertake the assignment at short notice.
5	Result	The order was lost

Case History 3: No External support for calibration of equipments

1	Company	New Company aiming US FDA approval
2	Incident:	FDA visiting for inspection in 4 weeks
3	Problems	Calibration / validation of analytical equipments were due over a long time. There was no approved vendor/consultant on the record to undertake the activity
4	Result	The audit failed

Case History 4: No External Support for ICH Documentation

1	Company	Formulation Unit (Anticancer products)
2	Incident:	Method Validation, Impurity profiling and stability studies were not as per ICH guidelines.
3	Problem:	Expert staff has no idea of ICH documentation. Further, there was no external supported for the same.
4	Result	The orders was cancelled

Case History 5: No External support for HVAC Validation

1	Company	Bulk Drug Unit
2	Incident	HVAC validation pending over 2 years
3	Problem	In adequate knowledge about HVAC validation. No external Advise available
4	Result	Severe complaints of product contamination with environmental dust and bioburden.

Case History 6: No External Support for cGMP Compliance

1	Company	Bulk Drugs and Drug Intermediate
2	Incident	cGMP compliance pending over 10 years
3	Problem	Insufficient QA staff for cGMP compliance. No experienced regulatory consultant on record.
4	Result	The company got black listed for Government Tenders

MISTAKE 5: ERRORS IN SOURCING RAW MATERIALS

Raw material play is a critical quality component of drug products. They shall be properly sourced, transported, received, stored, tested, and released for batch manufacturing. The vendor shall be capable of manufacturing and supplying the same under cGMP environment. Further he shall be able to deliver entire ordered quantity meeting all pharmacopoeia and special specifications.

Normally, following errors are noted in sourcing raw materials:

1	Sourcing from finicality unstable vendors who fail to stock required quantities and deliver the same in time.

2	Too much negotiation on price, quality and delivery schedule. This upsets the vendor and the delivery becomes erratic.
3	Accepting poor packaging
4	Incomplelete Specifications

Case History 1: Too much breakage

1	Company	I.V. solution unit (Glass Bottles)
2	Purchase	Empty I.V bottles.
3	Error	The supplier used secondhand corrugated boxes for packaging the products .The breakage in transit was more than 10% against normal 1%
4	FMA	Too much negotiation on the prices

Case History 2: Failure in Quality Compliance

1	Company	Injectable unit
2	Purchase	Ranitidine HCl B.P. suitable for I.V. injection.
3	Problem	The material passed B.P. but the end product failed in Endotoxins contents.
4	FMA	The supplier had failed in providing specifications for Endotoxins contents

Case History 3: Failure to identify suitable vendor

1	Company	Injectable Unit
2	Purchase	1200.00 kg of Ciprofloxacin HCl
3	Problem encounter	The first few batches of Ciprofloxacin HCl IV solution passed. However, remaining batches failed for endotoxins contents and assay.
4	FMA:	The supplier had actually sourced the material from 3 different manufactures having varying endotoxins contents and assay

Case History 4: Dissatisfaction on negotiated price

1	Company	Ayuervedic Drug Unit
2	Purchase	Herbal Extract
3	Problem:	The product failed in Quality specifications
4	FMA	Failure to make previous payments in time and bad relations

Case History 5: Dissatisfaction on negotiated price:

1	Company	Formulation Unit
2	Purchase r	Supply of Ofloxacin.
3	Problem	The vendor supplied 10 drums of Ofloxacin mixed within 2 drums of sodium chloride.
4	FMA:	The order was booked below the cost price. The price was further negotiated while making advance payments

Case History 6: Hard negotiation on logistics

1	Company	Formulation unit
2	Purchase	Ciprofloxacin Lactate IV Grade
3	Problem	To meet urgency the vendor loaded the material in a vehicle carrying turmeric bags. On delivery heavy contamination of turmeric was observed in drug product.
4	FMA	Hard negotiation on logistics

Advise:

1	Obtain raw materials directory from well established manufacturers.
2	Avoid agents as far as possible.
3	Do not change vendors frequently
4	Always provide detailed specifications along with PO State both in-house and pharmacopoeia norms
5	Pay attention on logistics
6	Insist supply in dedicated vehicles
7	Insist for packaging's as specified in PO

MISTAKES 6: MISSING USEFUL ASSOCIATION

GMP is achieved in steps and stages. You may climb few stages successfully. However, if attention is lost, you may fall many steps back. All your efforts and money will be wasted. The good association of persons is absolutely necessary for avoiding errors in cGMP compliance
It is considered as stroke of good luck if you succeed in associating with good persons/organizations as per below:

1	Association with Highly faithful, experienced , hard working and intelligent persons at key post

2	Association with Highly efficient vendors for supply and maintenance of equipments
3	Association with Highly genuine and true raw material vendors
4	Association with good regulatory consultants
5	Association with good past FDA Inspectors/directors
6	Association with well experienced colleagues

MISTAKE 7: FAILURE IN TIME MANAGEMENT

One of the most common errors in GMP is time miss-management. It has been generally noted that:

1	Workmen carry their personal problems at work and resolve / research on them during work
2	Some key persons develop job insecurity and work with 50% mind. The rest 50% remained focus on new opening.
3	Man people work more on maintaining their job rather than GMP. They spend more time on pleasing bosses and co workers.
4	Key person's donor stick to the assigned time. They enter at the site at any time and fly away without notice.
5	Key people loose 70 – 80% of their time in conducting meetings with visitors and workmen. They really do not have adequate time to concentrate on GMP.
6	Some management allows distracting activities like celebration of birthdays, mini parties on regular basis.
7	Some management believes in exhaustive reporting. Key people remain engrossed in the same and they do not know where GMP is moving.

Some of the Case History of time mismanagement is as per below:

Case History 1: Time for GMP 0 Hours

1	Site	Parenteral Unit
2	Personal	Production Manager
3	Duty Hours	10.00 am to 8.00 pm
4	Time breakup	Production 4 hrs Online trading in shares – 6 hrs GMP – 0 Hrs
5	Comments	Sometimes he is very liberal in GMP when trading is in his favor. However, he used to be very angry when the market is against him.

Case History 2: Time for GMP 0 Hours

1	Site	Bulk Drug Unit
2	Personal	Technical Director
3	Duty Hrs	10.00 am to 6.00 pm
4	Time breakup	Health – unfit for 2 hrs Production – 2 hrs Void discussion – 3 hrs R&D – 1 Hrs GMP – 0 Hrs

Case History 3: Time for GMP 0 Hours

1	Site	Excipient Unit
2	Personal	Technical Director
3	Duty Hour	10.00 am to 6.00 pm
4	Breakup	Plant Visit = 0 Hrs Scolding to staff = 3 hrs Finance =2 hrs, Miscellaneous =1 hrs GMP = 0 Hrs

Case History 4: Time for GMP just 2 Hours a day

1	Site:	Bulk Drug Unit (Mumbai)
2	Personal:	Lady Managing Partner
3	Duty	8 Hours + Extra 2 Hours
4	Breakup:	Production =8 Hrs, GMP = 2 Hrs

Case History 5: Time for GMP just 4 Hours a day

1	Site	Bulk Drug unit at Rajkot
2	Personal	Plant In charge
3	Duty	8 Hour + Extra 4 Hours
4	Breakup	Production = 8 Hour, GMP = 4 Hrs

MISTAKE 8: FAILURE IN DESIGNING AND MAINTENANCE FACILITIES

Common errors encountered in facility design and maintenance:

1.	Electrical load is much less than required.
2.	There is no stand by generator to run critical machines in the event of power failure or to meet excess requirement.
3.	Site is planned on unclean and uneven piece of land.
4.	Site surrounded by filth and waste water pools which support breeding of mosquitoes
5.	Machines are second hand and outdated.
6.	Walls and ceiling coatings are peeling off
7.	Heavy dampness and bacterial growth.
8.	No HVAC system.
9.	Dusting in Surroundings
10.	Ageing of building(cracks, holes and fissures in walls and ceiling)
11.	Hazardous installation of machines with no cleaning and maintenances space around
12.	Water stagnation at various points

Case History 1: Failure in designing Power Units

1	Facility	Parenteral Unit
2	Error	No stand by generator
3	Problem	Power failed during sterilization. The batch was resterilized which resulted in undue degradation of the drug

Case History 2: Failure in Validation of Water system

1	Site	Liquid Oral Dept.
2	Error	Water system being in-effective
3	Problem	A batch of liquid oral developed off odor and required rejection within 15 days
4	FMA:	They error was with DM Water which had very high bacterial count

Case History 3: Failure in Sanitation and Hygiene

1	Site	Manufacturing sugar based drug pellets
2	Error	Surroundings unhygienic
3	Problem	Production area was often found flooded with crawling insects and cockroaches

Case History 4: Failure in Validation of HVAC system

1	Site:	Bulk Drug Unit

2	Facility:	No HVAC System
3	Error:	Unguarded ventilators
4	Problem:	Many occasions dead birds were observed in the reactor

Case History 5: Failure in Maintenance of Machines

1	Site	Tablet manufacturing unit
2	Error	Very old machines
3	Problem	Regular metal contamination in the products

Case History 6: Failure in Designing the Facility

1	Site	Bulk Drug Unit
2	Error	Site on uneven piece of land
3	Problem	Heavy water logging in rainy season

Case History 7

1	Site	Formulation unit
2	Error	Hazardous layout
3	Problem	Mixing of unapproved materials with approved ones.

LEARNINGS

1	GMP is like insurance. It ensures efficacy and safety in the products. However, do not stretch it too much. Maintain it in good in limits. Over stretching will break.
2	First manage your team. If your team is properly oriented the GMP will be complied easily.
3	Teach people to shoulder responsibilities.
4	Take commitments for cGMP compliance.
5	Perform GMP reviews.
6	Ensure that entire team including vendors, contract analytical lab, calibration institutes, casual workmen distributors, transporters and warehouse follow and value GMP.
7	Always search and appoint qualified, experienced and genuine key persons at the site. Just donor appoints persons on Paper value.
8	Retain the genuine person on their terms. Just one key dynamic and genuine person can ensure more than 50% GMP compliance with resources and management support.
9	Always maintain data bank of genuine key persons.
10	Meet them during conferences and explore their potential for future employment. Remember that the genuine people are not always available through

	advertisements. You have to work and discover them.
11	Money is key factor for success in GMP. You have to budget the compliance. The funds shall be ready as and when needed. If you miss the payouts in time the work may get delayed resulting in unrecoverable set backs
12	Always built contingencies as you may be required to overspend to meet new regulations
13	Prioritize least expensive tasks like documentation, internal audits and internal training..
14	Never negotiate too hard with consultants and vendors as this will discourage them for positive inputs
15	Remember that GMP requires continuous vigilance.
16	Remember that deviation and change is the most common feature even with trained individuals. Avoid them totally.
17	Please note that people have tendency to ignore GMP. If one person ignores GMP successfully the other follows him and the trends spread up like a fire.
18	You must devote 100% of time for work as per GMP.
19	No personal talks. No jokes. No personal business.
20	No unnecessary meetings.
21	Be on the work and manage your entire time for GMP. Resist if some body instigates you for GMP deviations
22	Your facility shall be continuously updated.
23	You must ensure that processing, transportation are storage are meet the continuously growing production and QC/QA activities.
	End of Document