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## Good Practices in Production Facilities as Per Various Regulatory Guidelines in Pharmaceutical and Biotech Industry



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**Keywords:** WHO, Schedule M of D and C Act, USFDA, MHRA, TGA.

## ABSTRACT

The factory building(s) for manufacture of drugs shall be so situated and shall have such measures as to avoid risk of contamination from external environment including open sewage, drain, public lavatory or any factory which produce disagreeable or obnoxious odor or fumes, excessive soot, dust, smoke, chemical or biological emissions. Current study is aimed at requirements of Facilities and Equipment as per the different regulatory guidelines viz., WHO, Schedule M of D and C Act, USFDA, MHRA, TGA.

## **INTRODUCTION**

Each of the selected guidelines describes the requirement of Facilities and Equipment under the different chapters as below.

**WHO** describes the Production in Annexure 3 **WHO** good manufacturing practices for pharmaceutical products: Good practices in production

Schedule M describes the Production in PART 1 Good Manufacturing Practices for Premises and Materials of Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products - 3. Production area

USFDA describes the Production in PART 211— Current Good Manufacturing Practice for Finished Pharmaceuticals-CFR Title 21 Chapter I Subchapter C Part 211 Subpart F— Production and process control

MHRA describes the Production in Section II – 2EU Guidance on Good Manufacturing Practice (GMP) - Production

TGA/PICS describes the Production in CHAPTER 5 - Production

Detailed comparison of the selected guidelines with respect to Good practices in productionismadeinbelowtable:

Table 1: Comparison of regulatory guidelines for Production in pharmaceuticalindustry

WHO	Schedule M	USFDA	MHRA	TGA/PICS
WHO describes	Schedule M	USFDA describes	MHRA	TGA/PICS
the Production in	describes the	the Production in	describes the	describes the
Annexure 3	Production in	PART 211—	Production in	Production in
WHOgoodmanufacturingpracticesforpharmaceuticalproducts:Goodpracticesinproduction1	PART 1 Good Manufacturi ng Practices For Premises And Materials of	CurrentGoodManufacturingPracticeforFinishedPharmaceuticalse-CFR Title 21Chapter	Section II – 2EU Guidance On Good Manufacturin g Practice (GMP)	CHAPTER 5 Production <sup>5</sup>

WHO	Schedule M	USFDA	MHRA	TGA/PICS
	Good Manufacturi ng Practices And Requirement s of Premises, Plant And Equipment For For Pharmaceuti	I Subchapter C Part 211 Subpart F — Production and process control <sup>3</sup>	Production <sup>4</sup>	
16. Good practices in	3. Production area:	Production and process control	5. PRODUCTIO	Chapter 5 PRODUCTIO
production	<b>3.1.</b> The	211.100 Written	Ν	Ν
16.1Principle	production	procedures;	Principle	Principle
Production	area shall be	deviations.	Production	Production
operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, With the objective of obtaining products of the requisite quality.	designedtoallowtheproductionpreferablyinuni-flowandwithlogicalsequenceofoperations. <b>3.2.</b> In ordertoavoidtheriskofcross-	(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		operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain

WHO	Schedule M	USFDA	MHRA	TGA/PICS
WHO General 16.2 All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labeling, dispensing, processing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary,	Schedule Mdedicated andself-containedfacilities shallbemadeavailablefortheproductionofsensitivepharmaceuticalproductslikepenicillinorbiologicalpreparationswithlivemicro-organisms.Separatededicatedfacilitiesshallbeprovidedforthe	include all requirements in this subpart. These written procedures, including any changes, shall be	quality and bein accordancewith therelevantmanufacturingand marketingauthorisations.General5.1Productionshould beperformed andsupervised bycompetentpeople.5.2Allhandling ofmaterials and	andbeinaccordancewiththerelevantmanufacturingandmarketingauthorisations.GENERAL5.1.Productionshouldbeperformedandsupervisedbycompetentpeople.5.2.Allhandlingofmaterialsandproducts,such
accordance with written procedures or instructions and,	facilities shall be provided for the	followed in the execution of the various production	<b>5.2</b> All handling of	handling of materials and

WHO	Schedule M	USFDA	MHRA	TGA/PICS
wHO done in accordance with an approved procedure. The authorization of the deviation should be approved in writing by a	substances. 3.3. Working and in- process space shall be adequate to	USFDA         and justified.         211.101 Charg- in of components.         in of components.         Written production and control procedures shall	MHRA distribution should be done in accordance with written procedures or instructions and, where	TGA/PICS should be done in accordance with written procedures or instructions and, where necessary,
designated person, with the involvement of the QC department, when appropriate. <b>16.4</b> Checks on	permit orderly and logical positioning of equipment and materials and movement of	include the following, which are designed to assure that the drug products produced have the identity strength	necessary, recorded. <b>5.3</b> All incoming	recorded. <b>5.3.</b> All incoming materials should be checked to
yields and reconciliation of quantities should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits. <b>16.5</b> Operations on different products should not be	personnel to avoid cross- contamination and to minimize risk of omission or wrong application of any manufacturin g and control measures.	identity, strength, quality, and purity they purport or are represented to possess: (a) The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active	materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labeled with the prescribed	ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labeled with the prescribed data.
carriedoutsimultaneouslyorconsecutivelyinthe same roomorarea unless there is	<b>3.4.</b> Pipe-work, electrical fittings, ventilation	ingredient. (b) Components for drug product manufacturing shall be weighed,	data. <b>5.4</b> Damage to containers and any other problems	any other problem which might adversely affect the quality of a

WHO	Schedule M	USFDA	MHRA	TGA/PICS
no risk of mix up	openings and	measured, or	which might	material should
or cross-	similar	subdivided as	adversely	be investigated,
contamination.	service lines	appropriate. If a	affect the	recorded and
or cross- contamination. 16.6 At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate, the rooms and packaging lines being used should be labeled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and the batch number. Where applicable, this indication should also	similar	subdivided as appropriate. If a component is removed from the original container to another, the new container shall be identified with the following information: (1) Component name or item code; (2) Receiving or control number; (3) Weight or measure in new container; (4) Batch for which component was dispensed, including its product name, strength, and lot number.	adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department. 5.5Incoming materials and finished products should be physically or administrativel y quarantined immediately after receipt or processing until they have been released for use or	be investigated, recorded and reported to the Quality Control Department. <b>5.5</b> . Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing until they have been released for use or distribution.
of production. In		(c) Weighing,	distribution.	receipt as
some cases, it may				_
be useful to also		measuring, or subdividing	<b>5.6</b> Intermediat	though they
record the name of		operations for	e and bulk products	were starting
the previous			products	materials.

WHO	Schedule M	USFDA	MHRA	TGA/PICS
product that has		components shall	purchased as	<b>5.7.</b> All
been processed.		be adequately	such should be	materials and
16.7 Access to		supervised. Each	handled on	products should
production		container of	receipt as	be stored under
premises should be		component	though they	the appropriate
restricted to		dispensed to	were starting	conditions
authorized		manufacturing	materials.	established by
personnel.		shall be examined	<b>5.7</b> All	the
<b>16.8</b> Normally,		by a second person	materials and	manufacturer
non-medicinal		to assure that:	products	and in an
products should		(1) The component	should be	orderly fashion
not be produced in		was released by	stored under	to permit batch
areas or with		the quality control	the appropriate	segregation and
equipment destined		unit;	conditions	stock rotation.
for the production		(2) The weight or	established by	5.8. Checks on
of pharmaceutical		measure is correct	the	yields and
products.		as stated in the	manufacturer	reconciliation
-		batch production	and in an	of quantities
<b>16.9</b> In-process		records;	orderly fashion	should be
controls are usually performed within		(2) The containers	to permit batch	carried out as
1		(3) The containers	segregation	necessary to
the production area. The		are properly identified. If the	and stock	ensure that
area. The performance of		weighing,	rotation.	there are no
such in-process			5.8Checks on	discrepancies
controls should not		measuring, or subdividing	yields and	outside
have any negative		U U	reconciliation	acceptable
effect on the		operations are performed by	of quantities	limits.
quality of the		automated	should be	5.9. Operations
product or another		equipment under	carried out as	on different
product (e.g. cross		§211.68, only one	necessary to	products should
product (c.g. c1088		\$211.00, Only One		

WHO	Schedule M	USFDA	MHRA	TGA/PICS
contamination or		person is needed to	ensure that	not be carried
mix up).		assure paragraphs	there are no	out
Prevention of		(c)(1), (c)(2), and	discrepancies	simultaneously
cross-		(c)(3) of this	outside	or
contamination		section.	acceptable	consecutively
and bacterial		(d) Each	limits.	in the same
contamination		component shall	<b>5.9</b> Operations	room unless
during		either be added to	on different	there is no risk
production		the batch by one	products	of mix-up or
<b>16.10</b> When dry		person or verified	should not be	cross-
materials and		by a second person	carried out	contamination.
products are used		or, if the	simultaneously	<b>5.10.</b> At every
in production,		components are	or	stage of
special precautions		added by	consecutively	processing,
should be taken to		automated	in the same	products and
prevent the		equipment under	room unless	materials
generation and		§211.68, only	there is no risk	should be
dissemination of		verified by one	of mix-up or	protected from
dust. Provision		person.	cross-	microbial and
should be made for		211.103 Calculat	contamination.	other
proper air control		ion of yield.	<b>5.10</b> At every	contamination.
(e.g. supply and		Actual yields and	stage of	<b>5.11.</b> When
extraction of air of		percentages of	processing,	working with
suitable quality).		theoretical yield	products and	dry materials
16.11		shall be	materials	and products,
Contamination of a		determined at the	should be	special
starting material or		conclusion of each	protected from	precautions
of a product by		appropriate phase	microbial and	should be taken
another material or		of manufacturing,	other	to prevent the
product must be		processing,	contamination.	generation and

WHO	Schedule M	USFDA	MHRA	TGA/PICS
avoided. This risk		packaging, or	<b>5.11</b> When	dissemination
of accidental cross-		holding of the drug	working with	of dust. This
contamination		product. Such	dry materials	applies
arises from the		calculations shall	and products,	particularly to
uncontrolled		either be	special	the handling of
release of dust,		performed by one	precautions	highly active or
gasses, particles,		person or	should be	sensitizing
vapors, sprays or		independently	taken to	materials.
organisms from		verified by a	prevent the	<b>5.12.</b> At all
materials and		second person, or,	generation and	times during
products in		if the yield is	dissemination	processing, all
process, from		calculated by	of dust. This	materials, bulk
residues on		automated	applies	containers,
equipment, from		equipment under	particularly to	major items of
intruding insects,		§211.68, be	the handling of	equipment and
and from		independently	highly active	where
operators' clothing,		verified by one	or sensitizing	appropriate
skin, etc. The		person.	materials.	rooms used
significance of this		211.105 Equipm	<b>5.12</b> At all	should be
risk varies with the		ent identification.	times during	labeled or
type of		(a) All	processing, all	otherwise
contaminant and of			materials, bulk	identified with
the product being		compounding and storage containers,	containers,	an indication of
contaminated.		<b>U</b>	major items of	the product or
Among the most			equipment and	material being
hazardous		and major equipment used	where	processed, its
contaminants are		equipment used during the	appropriate	strength (where
highly sensitizing		production of a	rooms used	applicable) and
materials,		batch of a drug	should be	batch number.
biological		product shall be	labeled or	Where
preparations such			otherwise	applicable, this

WHO	Schedule M	USFDA	MHRA	TGA/PICS
as living		properly identified	identified with	indication
organisms, certain		at all times to	an indication	should also
hormones,		indicate their	of the product	mention the
cytotoxic		contents and, when	or material	stage of
substances, and		necessary, the	being	production.
other highly active		phase of	processed, its	<b>5.13.</b> Labels
materials.		processing of the	strength	applied to
Products in which		batch.	(where	containers,
contamination is		(b) Major	applicable)	equipment or
likely to be most		equipment shall be	and batch	premises should
significant are		identified by a	number.	be clear,
those administered		distinctive	Where	unambiguous
by injection or		identification	applicable, this	and in the
applied to open		number or code	indication	company's
wounds and those		that shall be	should also	agreed format.
given in large		recorded in the	mention the	It is often
doses and/or over a		batch production	stage of	helpful in
long time.		record to show the	production.	addition to the
16.12 Cross-		specific equipment	5.13 Labels	wording on the
contamination		used in the	applied to	labels to use
should be avoided		manufacture of	containers,	colors to
by taking		each batch of a	equipment or	indicate status
appropriate		drug product. In	premises	(for example,
technical or		cases where only	should be	quarantined,
organizational		one of a particular	clear,	accepted,
measures, for		type of equipment	unambiguous	rejected, clean).
example:		exists in a	and in the	<b>5.14.</b> Checks
(a) carrying out		manufacturing	company's	should be
production in		facility, the name	agreed format.	carried out to
dedicated and self-		of the equipment may be used in	It is often	ensure that

WHO	Schedule M	USFDA	MHRA	TGA/PICS
contained areas		lieu of a distinctive	helpful in	pipelines and
(which may be		identification	addition to the	other pieces of
required for		number or code.	wording on the	equipment used
products such as		211.110 Samplin	labels to use	for the
penicillins, live		g and testing of	colors to	transportation
vaccines, live		in-process	indicate status	of products
bacterial		materials and	(for example,	from one area
preparations and		drug products.	quarantined,	to another are
certain other			accepted,	connected in a
biologicals);		(a) To assure batch uniformity and	rejected, clean)	correct manner.
(b) conducting		integrity of drug	5.14 Checks	<b>5.15.</b> Any
campaign		products, written	should be	deviation from
production		procedures shall be	carried out to	instructions or
(separation in time)		established and	ensure that	procedures
followed by		followed that	pipelines and	should be
appropriate		describe the in-	other pieces of	avoided as far
cleaning in		process controls,	equipment	as possible. If a
accordance with a		and tests or	used for the	deviation
validated cleaning		examinations to be	transportation	occurs, it
procedure;		conducted on	of products	should be
(c) providing		appropriate	from one area	approved in
appropriately		samples of in-	to another are	writing by a
designed airlocks,		process materials	connected in a	competent
pressure		of each batch.	correct	person, with the
differentials, and		Such control	manner.	involvement of
air supply and		procedures shall be	<b>5.15</b> Any	the Quality
extraction systems;		established to	deviation from	Control
(d) minimizing the		monitor the output	instructions or	Department
risk of		and to validate the	procedures	when
contamination		performance of	should be	appropriate.

WHO	Schedule M	USFDA	MHRA	TGA/PICS
caused by		those	avoided as far	<b>5.16.</b> Access to
recirculation or re-		manufacturing	as possible. If	production
entry of untreated		processes that may	a deviation	premises should
or insufficiently		be responsible for	occurs, it	be restricted to
treated air;		causing variability	should be	authorized
(e) wearing		in the	approved in	personnel.
protective clothing		characteristics of	writing by a	<b>5.17.</b> Normally,
where products or		in-process material	competent	the production
materials are		and the drug	person, with	of non-
handled;		product. Such	the	medicinal
(f) using cleaning		control procedures	involvement of	products should
		shall include, but	the Quality	be avoided in
and decontamination		are not limited to,	Control	areas and with
procedures of		the following,	Department	the equipment
known		where appropriate:	when	destined for the
effectiveness;		(1) Tablet or	appropriate.	production of
		capsule weight	5.16 Access to	medicinal
(g) using a "closed		variation;	production	products.
system" in		(2) Disintegration	premises	PREVENTIO
production;		time;	should be	N OF CROSS-
(h) testing for			restricted to	CONTAMINA
residues;		(3) Adequacy of	authorized	TION IN
(i) Using		mixing to assure	personnel.	PRODUCTIO
cleanliness status		uniformity and	<b>5.17</b> Normally,	N N
labels on		homogeneity;	the production	
equipment.		(4) Dissolution	of non-	5.18.
		time and rate;	medicinal	Contamination
16.13 Measures to		(5) Clarity,	products	of a starting
prevent cross-		completeness, or	should be	material or of a
contamination and		pH of solutions.	avoided in	product by
their effectiveness		F		another

WHO	Schedule M	USFDA	MHRA	TGA/PICS
should be checked		(6) Bioburden	areas and with	material or
periodically		testing.	the equipment	product must be
according to SOPs.		(b) Valid in-	destined for	avoided. This
16.14 Production		process	the production	risk of
areas where		specifications for	of medicinal	accidental
susceptible		such	products.	cross-
products are		characteristics	Prevention of	contamination
processed should		shall be consistent	Cross-	arises from the
undergo periodic		with drug product	contaminatio	uncontrolled
environmental		final specifications	n in	release of dust,
monitoring (e.g.		and shall be	Production	gasses, vapors,
for microbiological		derived from	5.18	sprays or
monitoring and		previous	Contamination	organisms from
particulate matter		acceptable process	of a starting	materials and
where appropriate).		average and	material or of	products in
		process variability	a product by	process, from
December		estimates where	another	residues on
Processing		possible and	material or	equipment, and
operations		determined by the	product must	from operators'
16.15 Before any		application of	be avoided.	clothing. The
processing		suitable statistical	This risk of	significance of
operation is		procedures where	accidental	this risk varies
started, steps		appropriate.	cross-	with the type of
should be taken to		Examination and	contamination	contaminant
ensure that the		testing of samples	arises from the	and of product
work area and		shall assure that	uncontrolled	being
equipment are		the drug product	release of dust,	contaminated.
clean and free from		and in-process	gasses, vapors,	Amongst the
any starting		material conform	sprays or	most hazardous
materials,		to specifications.	organisms	contaminants
products, product				are highly

WHO	Schedule M	USFDA	MHRA	TGA/PICS
residues, labels or		(c) In-process	from materials	sensitizing
documents not		materials shall be	and products	materials,
required for the		tested for identity,	in process,	biological
current operation.		strength, quality,	from residues	preparations
<b>16.16</b> Any		and purity as	on equipment,	containing
necessary in-		appropriate, and	and from	living
process controls		approved or	operators'	organisms,
and environmental		rejected by the	clothing. The	certain
controls should be		quality control	significance of	hormones,
carried out and		unit, during the	this risk varies	cytotoxics, and
recorded.		production	with the type	other highly
16.17 Maana		process, e.g., at	of contaminant	active
16.17Meansshould be instituted		commencement or	and of product	materials.
		completion of	being	Products in
of indicating failures of		significant phases	contaminated.	which
		or after storage for	Amongst the	contamination
equipment or of		long periods.	most	is likely to be
services (e.g.		(d) Rejected in-	hazardous	most significant
water, gas) to		process materials	contaminants	are those
equipment. Defective		shall be identified	are highly	administered by
equipment should		and controlled	sensitizing	injection, those
be withdrawn from		under a quarantine	materials,	given in large
use until the defect		system designed to	biological	doses and/or
has been rectified.		prevent their use in	preparations	over a long
After use,		manufacturing or	containing	time.
production use,		processing	living	<b>5.19.</b> Cross-
equipment should		operations for	organisms,	contamination
be cleaned without		which they are	certain	should be
delay according to		unsuitable.	hormones,	avoided by
detailed written		211.113 Control	cytotoxics and other highly	appropriate
			outer mgmy	technical or

WHO	Schedule M	USFDA	MHRA	TGA/PICS
procedures and		of microbiological	active	organizational
stored under clean		contamination.	materials.	measures, for
and dry conditions		(a) Appropriate	Products in	example:
in a separate area		written procedures,	which	a) production in
or in a manner that		designed to	contamination	segregated
will prevent		prevent	is likely to be	areas (required
contamination.		objectionable	most	for products
16.18 Time limits		microorganisms in	significant are	such as
for storage of		drug products not	those	penicillins, live
equipment after		required to be	administered	vaccines, live
cleaning and		sterile, shall be	by injection,	bacterial
before use should		established and	those given in	preparations
be stated and based		followed.	large doses	and some other
on data.		(b) Appropriate	and/or over a	biologicals), or
<b>16.19</b> Containers		written procedures,	long time.	by campaign
for filling should		designed to	<b>5.19</b> Cross-	(separation in
be cleaned before		prevent	contamination	time) followed
filling. Attention		microbiological	should be	by appropriate
should be given to		contamination of	avoided by	cleaning;
avoiding and		drug products	appropriate	b) providing
removing any		purporting to be	technical or	appropriate
contaminants such		sterile, shall be	organizational	airlocks and air
as glass fragments		established and	measures, for	extraction;
and metal particles.		followed. Such	example:	c) minimizing
<b>16.20</b> Any		procedures shall	(a) production	the risk of
significant		include validation	in segregated	contamination
deviation from the		of all aseptic and	areas (required	caused by
expected yield		sterilization	for products	recirculation or
should be recorded		processes.	such as	re-entry of
and investigated.		211.115 Reproce	penicillins,	untreated or

WHO	Schedule M	USFDA	MHRA	TGA/PICS
16.21Checksshould be carriedout to ensure thatpipelines and otherpiecesofequipment used forthe transportationof products fromone area to anotherare connected in acorrect manner.16.22Pipes usedforconveyingdistilledordeionizedwaterand,whereappropriate,otherwater pipes shouldonbe sanitized and	Schedule M	ssing.(a)Writtenprocedures shall beestablishedandfollowedandfollowedandprescribingasystemforreprocessingforbatches that do notforconformtostandardsorspecificationsandthestepstotaken to insure thatthethereprocessedbatcheswillconformwithandards,and	MHRA live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning; (b) providing appropriate airlocks and air extraction; (c) minimizing the risk of contamination caused by	TGA/PICSinsufficientlytreated air;d)kepingprotectiveclothing insideareaswhereproductswithspecial risk ofcross-contaminationare processed;e)usingcleaninganddecontaminationn procedures ofknowneffectiveness,asineffectivecleaningof
deionizedwaterand,whereappropriate,otherwater pipesshould		the reprocessed batches will conform with all established	(c) minimizing the risk of contamination caused by	n procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross- contamination; f) using "closed systems" of production; g) Testing for residues and

WHO	Schedule M	USFDA	MHRA	TGA/PICS
controlequipmentandinstrumentsshouldbeservicedandcalibratedatprespecifiedandandintervalsandandrecordsmaintained.Toensuresatisfactoryfunctioning,instrumentsshouldbebecheckeddaily orpriortouseperforminganalyticaltests.Thedateofcalibrationandservicingandthedatewhenrecalibration is dueshouldbeshouldbeclearlyindicated on a labelattachedto	Schedule M	USFDA	contamination are processed;(e)using cleaningcleaningand decontaminationproceduresofknown effectiveness,asineffective cleaningcleaningof equipmentsourceof cross- contamination;(f)using "closed systems"(g)Testing for residuesiseof contamination;	TGA/PICSequipment. $5.20.$ $Weasures$ to $prevent$ to $prevent$ cross- $their$ andtheireffectivenessshouldbecheckedperiodicallyaccording to setprocedures.ValidationstudiesshouldreinforceGoodManufacturingPracticeandwithdefinedprocedures.withdefinedprocedures.withdefinedprocedures.withdefinedprocedures.studiesand
analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label		HUMAN	cross- contamination; (f) using "closed systems" of production; (g) Testing for residues and	<b>5.21.</b> Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined
instrument. <b>16.24</b> Repair and maintenance operations should not present any hazard to the quality of the			status labels on equipment. <b>5.20</b> Measures to prevent cross- contamination and their	Resultsandconclusionsshouldberecorded.5.22. When anynewmanufacturingformulaor

WHO	Schedule M	USFDA	MHRA	TGA/PICS
products.			effectiveness	method of
Packaging			should be	preparation is
operations			checked	adopted, steps
<b>16.25</b> When the			periodically	should be taken
			according to	to demonstrate
1 0			set procedures.	its suitability
packaging				for routine
operations is being				processing. The
set up, particular				defined process,
attention should be			Validation	using the
given to			5.21	materials and
minimizing the risk			Validation	equipment
of cross-			studies should	specified,
contamination,			reinforce Good	should be
mix-ups or		and the	Manufacturing	shown to yield
substitutions.		HUMAN	Practice and be	a product
Different products		That in the	conducted in	consistently of
should not be			accordance	the required
packaged in close			with defined	quality.
proximity unless			procedures.	5.23.
there is physical			Results and	Significant
segregation or an			conclusions	amendments to
alternative system			should be	the
that will provide			recorded.	manufacturing
equal assurance.			<b>5.22</b> When any	process,
<b>16.26</b> Before				including any
packaging			new	change in
operations are			manufacturing	equipment or
begun, steps			formula or	materials,
should be taken to			method of	which may
ensure that the			preparation is	affect product

WHO	Schedule M	USFDA	MHRA	TGA/PICS
workarea,packaginglines,printingmachinesandotherequipmentareclean and free fromanyproducts,materialsordocumentsusedpreviouslyandwhicharenotrequiredforthecurrentoperation.The lineclearanceshouldbeperformedandaccordingtoappropriateandchecklistandrecorded.andandbatch numberoftheproductbeinghandled	Schedule M	USFDA	adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality. <b>5.23</b> Significant amendments to the manufacturing process, including any	quality and/orthereproducibilityof the process,should bevalidated.5.24. Processesand proceduresshould undergoperiodic criticalrevalidation toensure that theyremain capableof achieving theintendedresults.StartingMaterials5.25. Thepurchase ofstartingmaterials is animportantoperation which
procedureandchecklistandrecorded.16.27The nameandbatchnumberoftheproduct			<b>5.23</b> Significant amendments to the manufacturing process,	Materials5.25.Thepurchaseofstartingmaterialsisanimportant

WHO	Schedule M	USFDA	MHRA	TGA/PICS
filling and sealing			the	5.26. Starting
should be followed			reproducibility	materials
as quickly as			of the process	should only be
possible by			should be	purchased from
labeling. If			validated.	approved
labeling is delayed,			5.24 Processes	suppliers
appropriate			and procedures	named in the
procedures should			should	relevant
be applied to			undergo	specification
ensure that no mix			periodic	and, where
ups or mislabelling			critical re-	possible,
can occur.			validation to	directly from
16.29 The correct			ensure that	the producer. It
performance of any		1	they remain	is
printing (e.g. of		N. ANT	capable of	recommended
code numbers or		HUMAN	achieving the	that the
expiry dates) done			intended	specifications
separately or in the			results.	established by
course of the			Starting	the
packaging should			Materials	manufacturer
be checked and			5.25 The	for the starting
recorded. Attention			5.25 The	materials be
should be paid to			purchase of	discussed with
printing by hand,			starting	the suppliers. It
which should be			materials is an	is of benefit
rechecked at			important	that all aspects
regular intervals.			operation which should	of the
16.30 Special care				production and
should be taken			involve staff who have a	control of the
when cut labels are				starting
			particular and	material in

WHO	Schedule M	USFDA	MHRA	TGA/PICS
used and when			thorough	question,
overprinting is			knowledge of	including
carried out off-line,			the suppliers.	handling,
and in hand-			<b>5.26</b> Starting	labeling and
packaging			materials	packaging
operations. Roll			should only be	requirements,
feed labels are			purchased	as well as
normally			from approved	complaints and
preferable to cut			suppliers	rejection
labels in helping to			named in the	procedures, are
avoid mix ups.			relevant	discussed with
Online verification			specification	the
of all labels by			and, where	manufacturer
automated			possible,	and the
electronic means		N. AN	directly from	supplier.
can be helpful in		HUMAN	the producer.	<b>5.27.</b> For each
preventing mix			It is	delivery, the
ups, but checks			recommended	containers
should be made to			that the	should be
ensure that any			specifications	checked for
electronic code			established by	integrity of
readers, label			the	package and
counters, or similar			manufacturer	seal and for
devices are			for the starting	correspondence
operating correctly.			materials be	between the
When labels are			discussed with	delivery note
attached manually,			the suppliers.	and the
in-process control			It is of benefit	supplier's
checks should be			that all aspects	labels.
performed more			of the	<b>5.28.</b> If one
frequently.			production and	

WHO	Schedule M	USFDA	MHRA	TGA/PICS
16.31 Printed and			control of the	material
embossed			starting	delivery is
information on			material in	made up of
packaging			question,	different
materials should be			including	batches, each
distinct and			handling,	batch must be
resistant to fading			labeling and	considered as
or erasing.			packaging	separate for
16.32 Regular			requirements,	sampling,
online control of			as well as	testing and
the product during			complaints and	release.
packaging should			rejection	5.29. Starting
include at least			procedures,	materials in the
checks on:			are discussed	storage area
(a) the general		N. ANT	with the	should be
appearance of the		HUMAN	manufacturer	appropriately
packages;			and the	labeled (see
			supplier.	Chapter 5, Item
(b) whether the			5.27 For each	13). Labels
packages are			delivery, the	should bear at
complete;			containers	least the
(c) whether the			should be	following
correct products			checked for	information:
and packaging			integrity of	□ the
materials are used;			package and	designated
(d) whether any			seal and for	name of the
overprinting is			correspondenc	product and the
correct;			e between the	internal code
(e) the correct			delivery note	reference where
functioning of line			and the supplier's	applicable;

WHO	Schedule M	USFDA	MHRA	TGA/PICS
packaging			the internal	procedures or
materials and the			code reference	measures to
number of units			where	assure the
produced should be			applicable;	identity of the
investigated,			_ a batch	contents of each
satisfactorily			number given	container of
accounted for, and			at receipt;	starting
recorded before			-	material. Bulk
release.			_ where	containers from
16.35 Upon			appropriate,	which samples
completion of a			the status of	have been
packaging			the contents	drawn should
operation, any			(e.g. in	be identified
unused batch-			quarantine, on	(see Chapter 6,
coded packaging		NY MA	test,	Item 13).
materials should be		HUMAN	released,	<b>5.31.</b> Only
destroyed and the			rejected);	starting
destruction			_ where	materials which
recorded. A			appropriate, an	have been
documented			expiry date or	released by the
procedure			a date beyond	Quality Control
requiring checks to			which	Department and
be performed			retesting is	which are
before returning			necessary.	within their
unused materials			When fully	shelf-life
should be followed			computerized	should be used.
if uncoded printed			storage	<b>5.32.</b> Starting
materials are			systems are	materials
returned to stock.			used, all the	should only be
16.36 Production			above	dispensed by

WHO	Schedule M	USFDA	MHRA	TGA/PICS
records should be			information	designated
reviewed as part of			need not	persons,
the approval			necessarily be	following a
process of batch			in a legible	written
release before			form on the	procedure, to
transfer to the			label.	ensure that the
authorized person.			<b>5.30</b> There	correct
Any divergence or			should be	materials are
failure of a batch to			appropriate	accurately
meet production			procedures or	weighed or
specifications			measures to	measured into
should be			assure the	clean and
thoroughly			identity of the	properly
investigated. The			contents of	labeled
investigation		NY ANY	each container	containers.
should, if		HUMAN	of starting	<b>5.33.</b> Each
necessary, extend			material. Bulk	dispensed
to other batches of			containers	material and its
the same product			from which	weight or
and other products			samples have	volume should
that may have been			been drawn	be
associated with the			should be	independently
specific failure or			identified (see	checked and the
discrepancy. A			Section II,	check recorded.
written record of			Chapter6, item	5.34. Materials
the investigation			13).	dispensed for
should be made			<b>5.31</b> Only	each batch
and should include			starting	should be kept
the conclusion and			materials	together and
follow-up action.			which have	conspicuously

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			been released by the Quality Control Department and which are within their shelf life should be used. 5.32 Starting materials should only be dispensed by designated jersons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labeled containers.	Iabeled as such.ProcessingOperationsIntermediateAndBulkProductsS.35.Beforeanyprocessingoperationisstarted,stepsshould be takentoensuretheworkareaandindequipmentindanquiindanquiproductanquiineinaterials,products,operationinaterials,operationinaterials,inotinaterials,inotindinotindicesonindicesinot

Citation: Chagi Venkatesh et al. Ijsrm.Human, 2017; Vol. 5 (3): 61-120.

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			Image of the startingreader and freefrom anystartingmaterials,products,products,product of andresidues ordocuments notrequired forthe currentoperation.5.36Intermediateand bulkproductsshould be keptunderappropriateconditions.5.37Criticalprocessesshould bevalidated (see"VALIDATION" in thischapter).5.38Anynecessary in-processcontrols and	IGA/I ICScontrolofprimaryandprintedandpackagingmaterialsshouldbeaccordedattentionsimilarto thatgiven to startingmaterials.shouldbeattentiontogiven to startingmaterials.shouldbeattention shouldbeprintedtoprintedinadequatelysecureconditionssuchasto <exclude< td="">unauthorizedaccess.labelsand otherlooseprintedmaterialsshouldshouldbestoredandtaterialscutaccess.Cutlabels and otherlooseprintedmaterialssecureshouldbestoredandtransportedinseparateclosed</exclude<>

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			environmental         controls         should       be         should       be         carried out and         recorded.         5.39       Any         significant         deviation         deviation         the       expected         yield should       be         recorded       and         investigated       and         investigated       and         purchase,       The         handling       and         control       of         primary       and         printed       and         packaging       and         materials       shall         be       accorded         attention       similar to that         given       to         starting       materials.	containers so as         to avoid mix-         ups. Packaging         materials         should be         issued for use         only by         authorized         personnel         following an         approved and         documented         procedure.         following or         batch of primary         packaging         material should         be given a         specific         reference         number or         identification         mark.         5.43. Out-dated         or obsolete         primary         packaging         material or

WHO	Schedule M	USFDA	MHRA	TGA/PICS
		Image: A matrix of the second seco	should be paid         to       printed         materials.         They       should         be       stored         inadequately         secure         conditions         such as to         exclude         unauthorized         access.       Cut         labels       and         other       loose         printed       soose         stored       and         other       loose         printed       soose         should       be         should       be         stored       and         ransported       and         ransported       in         separate <closed< td="">       and         ransported       in         separate<closed< td="">       and         mix-ups.       so         Packaging       materials         should       be         issued       for         only       by         only       by         iauthorized       in         personnel       in</closed<></closed<>	printed           packaging           material should           be         destroyed           and         this           disposal         this           recorded.         Tecorded.           Packaging         this           fackaging         a           fackaging         a           fackaging         a           program for the         packaging           particular         then           particular         to           particular         to           minimizing the         to           risk of crossa         o           contamination,         mix           mix-ups or         substitutions.           Different         products should           not be packaged         in close           inot be packaged         proximity

approved and documented procedure.5.45.Before packaging operations are begun, steps should be taken to ensure that the work area, packaging materialbegun, steps should be taken to ensure that the work area, packaging materialmaterial should be given a specific reference mark.material should be equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be gereformed according to an appropriate checklist.should be given a specific reference primary packaging material or obsolee primary packaging material should be packaging material should be packaging material should be packaging material should be according to an appropriate checklist.for the current operation. The line-clearance should be destroyed and this disposal recorded.for the area and batch number of the	WHO	Schedule M	USFDA	MHRA	TGA/PICS
			Image: A set of the set	documented procedure. 5.42 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark. 5.43 Out-dated or obsolete primary packaging material or printed packaging material or printed packaging material or	packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, packaging lines, packaging lines, protining nachines and other equipment are from any products, naterials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate checklist.

WHO Schedule M	USFDA	MHRA	TGA/PICS
WHO Schedule M	USFDA	MHRAOperations5.44Whensettingupaprogramforthepackagingoperations,particularattentionbegiventominimizingtheriskofcontamination,mix-upsmix-upsorsubstitutions.Differentproductsshouldnotpackagedincloseproximityunlessthere isphysicalsegregation.5.45Beforepackagingoperationsarebegun,stepsshouldbe	TGA/PICS         product       being         handled       should         be       displayed         be       displayed         each       packaging         station or line.       All         products       and         products       and         packaging       materials         materials       be         identity       and         quantity,       and         identity       and         conformity with       the         the       Packaging         Instructions.       Stats.         Containers       for         filling       should         be       clean         should be given       for         filling.       Attention         should be given       and         contaminants       sno

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			that the work area, packaging lines, printingmachines andother andequipment areclean and freefrom anyproducts,materials ordocumentsordocumentspreviouslyused if theseare notrequired forthe currentoperation. Theline-clearanceshould beperformedaccording toan appropriatechecklist.5.46 The nameand batchnumber of theproduct beinghandled shouldbe displayed ateach	fragmentsandmetal particles.5.49.Normally,fillingandsealingshouldbefollowedasquicklyaspossiblebylabeling.If it isnotthecase,appropriateproceduresshouldbeappliedtoensurethatmix-upsormislabellingorcan occur.Thecorrectperformanceperformanceofanyprintingoperation(forexamplecodenumbers, expirydates)tototheorin the courseofthepackaging

WHO	Schedule M	USFDA	MHRA	TGA/PICS
WHO	Schedule M	USFDA	MHRApackagingstation or line.5.47Allproductsandpackagingmaterials to beused should becheckedondelivery to thepackagingdepartmentquantity,identityandconformitywiththePackagingInstructions.5.48Containersforfillingshould	TGA/PICSshouldbecheckedandrecorded.andAttentionandshouldbepaidtoprintingbyhandwhichshouldberecheckedatregularandintervals. <b>5.51.5.51.</b> Specialcareshouldusingcut-labelsandwhenoverprintingiscarriedoutline.Roll-feedlabelsare
		HUMAN	department for quantity, identity and conformity with the	<ul><li>intervals.</li><li><b>5.51.</b> Special care should be taken when using cut-labels</li></ul>
			<b>5.48</b> Containers for	carried out off- line. Roll-feed
			avoiding and removing any contaminants such as glass fragments and	<b>5.52.</b> Checks should be made to ensure that any electronic code readers,

WHO	Schedule M	USFDA	MHRA	TGA/PICS
WHO	Schedule M		MHRA metal particles. 5.49 Normally, filling and sealing should be followed as quickly as quickly as possible by labeling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur. 5.50 The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging	label       counters         or       similar         devices       are         operating       are         correctly.       5.53.         5.53.       Printed         and       embossed         information       on         packaging       and         should       be         distinct       and         resistant       to         fading       or         erasing.       5.54.         Should       of         packaging       should         should       of         information       and         resistant       to         fading       or         grackaging       or         should       include         packaging       should         should       include         at       least         checking       the

WHO	Schedule M	USFDA	MHRA	TGA/PICS
		Image: August and August	shouldbecheckedandrecorded.Attentionshould be paidtoto printing byhandhandwhichshould be re-atcheckedatregularintervals.5.51Specialcare should betakenusingcutlabelsandwhenoverprinting iscarried out off-line.Roll-feedlabelsarenormallypreferabletocutlabels, inhelpingtoavoid mix-ups.5.52Checksshouldbemade to ensurethatany	<ul> <li>c) whether the correct products and packaging materials are used;</li> <li>d) whether any over-printing is correct;</li> <li>e) correct functioning of line monitors.</li> <li>Samples taken away from the packaging line should not be returned.</li> <li>5.55. Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorized personnel.</li> </ul>
WHO	Schedule M	USFDA	MHRA	TGA/PICS
-----	------------	-------	--	--
		USFDA	NHRAare complete;(c) whether the correctproducts and packagingmaterials are used;(d) whether any over- printing is correct;(e) correct functioning of line monitors.Samples taken away from the packaging line should not be returned.5.55 Products which have been involved in an unusual event should only be reintroduced into the process after special	IGA/PICSmaterialsshouldbedestroyed andthe destrutionrecorded.Adocumentedprocedureprocedureshouldbefollowedifdocumentedarefollowedarefollowedarereturnedtostock.toFinishedFoductsfollowedingroductsingroductsingroductsinineirfinalreleaseunderineirfinalineirfinalineirfinalineirfinalineirfinalineirfinalineirfinalineirfinalineirfinalineirfinalineirfinalineirfinalineirinineirfinalineirinineirinineirinineirinineirin

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			inspection,	which is
			investigation	necessary
			and approval	before releasing
			by authorized	of product for
			personnel.	sale are
			Detailed	described in
			record should	Chapter 6
			be kept of this	(Quality
			operation.	Control).
			<b>5.56</b> Any	<b>5.60.</b> After
			significant or	release, finished
			unusual	products should
			discrepancy	be stored as
		1.	observed	usable stock
		N. The	during	under
		HUMAN	reconciliation	conditions
			of the amount	established by
			of bulk	the
			product and	manufacturer.
			printed	Rejected,
			packaging	recovered and
			materials and	returned
			the number of	materials
			units produced	5.61. Rejected
			should be	materials and
			investigated	products should
			and	be clearly
			satisfactorily	marked as such
			accounted for	and stored
			before release.	
				separately in

5.57 Upon restricted areas.   completion of They should   a packaging either be   operation, any returned to the   unused batch- suppliers or,   coded where   packaging appropriate,   materials reprocessed or   should be destroyed.   Whatever action is taken   recorded. A   documented approved and   procedure recorded by   should be authorized   personnel. coded printed   coded printed personnel.   code. stock.   Finished be exceptional.   Products It is only   permitted if the quality of the   final product is anot affected, if   in quarantine until their final   relevae moder
release under specifications conditions are met and if it established by is done in accordance

WHO	Schedule M	USFDA	MHRA	TGA/PICS
	Schedule M	USFDA	MHRAthemanufacturer. $5.59$ TheevaluationoffinishedofproductsanddocumentationwhichisnecessarybeforereleaseofproductsalearedescribedinChapter6(QualityControl). $5.60$ Afterrelease,finishedproductsshouldshouldbestoredasusablestockunderconditionsestablishedbythemanufacturerRejected,Recovered	with a defined and authorized procedure after evaluation of the risks involved. Record should be kept off the reprocessing. 5.63. The

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			and Returned	evaluation of
			Materials	the risks
			5.61 Rejected	involved,
			materials and	including any
			products	possible effect
			should be	on shelf life.
			clearly marked	The recovery
			as such and	should be
			stored	recorded.
			separately in	<b>5.64.</b> The need
			restricted	for additional
			areas. They	testing of any
			should either	finished
		*	be returned to	product which
		N. L. Martin	the suppliers	has been
		HUMAN	or, where	reprocessed, or
			appropriate,	into which a
			reprocessed or	recovered
			destroyed.	product has
			Whatever	been
			action is taken	incorporated,
			should be	should be
			approved and	considered by
			recorded by	the Quality
			authorized	Control
			personnel.	Department.
			<b>5.62</b> The	5.65. Products
			reprocessing	returned from
			of rejected	the market and
			products	which have left

should be the control of exceptional. It the is only manufacturer permitted if should be the quality of destroyed the final unless without product is not doubt, their affected, if the quality is specifications satisfactory; are met and if they may be it is done in considered for accordance resale, re- with a defined labeling or and authorized recovery with a procedure after subsequent evaluation of batch only after the risks they have been involved. critically Record should assessed by the be kept off the Quality Control reprocessing. Department in accordance with a written
or part of procedure. The nature of the which conform product, any to the required quality by conditions it incorporation requires, its

WHO Schedule M USFD	A MHRA	TGA/PICS
WHO Schedule M USFD   Image: Schedule M Image: Schedule M Image: Schedule M   Image: Schedule M Image: Schedule M Image: Schedule M   Image: Schedule M Image: Schedule M Image: Schedule M   Image: Schedule M Image: Schedule M Image: Schedule M   Image: Schedule M Image: Schedule M Image: Schedule M   Image: Schedule M Image: Schedule M Image: Schedule M   Image: Schedule M Image: Schedule M Image: Schedule M   Image: Schedule M Image: Schedule M Image: Schedule M   Image: Schedule M Image: Schedule M Image: Schedule M   Image: Schedule M Image: Schedule M Image: Schedule M   Image: Schedule M Image: Schedule M Image: Schedule M   Image: Schedule M Image: Schedule M Image: Schedule M   Image: Schedule M Image: Schedule M Image: Schedule M   Image: Schedule M Image: Schedule M Image: Schedule M   Image: Schedule M Image: Schedule M Image: Schedule M   Image: Schedule M Image: Schedule M Image: Schedule M   Image: Schedule M Image: Sch	A MHRA product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded. 5.64 The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has	time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			been	
			incorporated,	
			should be	
			considered by	
			the Quality	
			Control	
			Department.	
			5.65 Products	
			returned from	
			the market and	
			which have	
			left the control	
			of the	
			manufacturer	
		N. ANT	should be	
		HUMAN	destroyed	
			unless without	
			doubt, their	
			quality is	
			satisfactory;	
			they may be	
			considered for	
			resale, re-	
			labelling or	
			recovery in a	
			subsequent	
			batch only	
			after they have	
			been critically	
			assessed by the	
			Quality	

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			Control	
			Department in	
			accordance	
			with a written	
			procedure. The	
			nature of the	
			product, any	
			special storage	
			conditions it	
			requires, its	
			condition and	
			history, and	
			Accepted by	
			venkat	
		No by	the time	
		HUMAN	elapsed since it	
			was issued	
			should all be	
			taken into	
			account in this	
			assessment.	
			Where any	
			doubt arises	
			over the	
			quality of the	
			product, it	
			should not be	
			considered	
			suitable for re-	
			issue or re-use,	
			15500 01 10-050,	

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			although basic	
			chemical	
			reprocessing to	
			recover active	
			ingredient may	
			be possible.	
			Any action	
			taken should	
			be	
			appropriately	
			recorded.	

# DISCUSSION

Based on the above comparative study of production controls in the pharmaceutical industry as per WHO, Schedule M of D and C act, USFDA, MHRA and TGA/PICS Good Manufacturing practice guidelines below are the discussion outcomes. Discussion is carried out under different heading for better understanding purpose.

# **Guidelines Chapters**

**WHO** describes the Production in Annexure **3WHO** good manufacturing practices for pharmaceutical products: Good practices in production

Schedule M: Schedule M describes the Production in PART 1 Good Manufacturing Practices for Premises and Materials of Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products

USFDA: USFDA describes the Production in PART 211— Current Good Manufacturing Practice for Finished Pharmaceuticals e-CFR Title 21Chapter I Subchapter C Part 211 Subpart F— Production and process control

MHRA: MHRA describes the Production in Section II – 2EU Guidance on Good Manufacturing Practice (GMP) Production

TGA/PICS: TGA/PICS describes the Production in CHAPTER 5Production

### Principle

Production and process controls in pharmaceutical industry work on the principle "Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and marketing authorizations."

### **Production Area and Construction features**

The production area shall be designed to allow the production preferably in uni-flow and with logical sequence of operations. Pipe-work, electrical fittings, ventilation openings and similar service lines shall be designed, fixed and constructed to avoid. Service lines shall preferably be identified by colors and the nature of the supply and direction of the flow shall be marked/indicated.

WHO describes the nature of construction features for production area in clause 16.22

Schedule M of D and C act describe this requirement under 3.1 and 3.4

Requirement of production area and construction features is not covered under subpart F – Production and process control of USFDA however same is covered under subpart C building and facilities.



MHRA and TGA/PICs describes this requirement under 5.14 however the detailed description for the area and construction features is covered under chapter 3 premises and equipment.

#### Access to production area

All the selected guidelines details about the access to production area, as per the guidelines, access to production area is restricted and only authorized personnel shall have the access.

WHO describe this requirement under clause 16.7.

Schedule M of D and C act describes this requirement under different chapters of the act.

MHRA and TGA/PICs covered this requirement under 5.16.

USFDA describe this requirement under 211.28 (c) of USFDA, this section is covered under requirement of personnel in pharmaceutical industry.

### Written procedures; deviations

All the activities related to production shall be as per the written procedures, requirement of written procedures are described under the different clauses of selected guidelines as follows

WHO describe the requirement of written procedures and deviations under clause 16.2 and 16.3.

Schedule M of Drugs and Cosmetic Act does not detail the requirement of written procedures under the chapter 3. Production area, however, this requirement is detailed under the different chapters of the act.

USFDA describes this requirement under 211.100 written procedures; deviations.

MHRA and TGA/PICs describes the requirement of written procedures under clause 5.2.

# Equipment

All the selected guidelines describe the requirement of equipment for production of drug products. The equipment should be installed, qualified and maintained in such a way to fulfill the requirement of product, all the equipment should be cleaned properly to avoid any cross contamination before start of manufacturing activity; same shall be verified and confirmed. The equipment shall be identified properly for its usage, calibration status, content along with date and sign of the personnel identified. If any defective equipment is identified same shall be isolated from the area with proper means or shall be labeled appropriately to avoid usage of such equipment.

# Starting and packing materials

The detailed requirement of raw materials or starting materials are given under different chapters of the selected guidelines, however, all the selected guidelines have not described this requirement under production and process control accordingly schedule M of D and C act describe this in chapter 10 Raw materials, WHO guidelines describe this under chapter 14 Materials.

USFDA describe the requirement of starting materials under 211.101 Charge-in of components.

MHRA and TGA/PICs guidelines describe the requirement of starting materials under section starting materials 5.25 to 5.34 and from 5.40 to 5.43 for packing materials.

#### Weighing and measurement

As per the guidelines selected for study, all the materials used in the production of drug products should be weighed accurately before charging in for production, the measuring, weighing, recording and control equipment and instruments should be serviced and calibrated at prespecified intervals and records of the same shall be maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label attached to the instrument.

### **Prevention of cross contamination**

The GMP guidelines selected for study describe the prevention of cross contamination by suitable means. All the guidelines emphasize on the subject under different sections as described below:

WHO describe this under **Prevention of cross-contamination and bacterial contamination during production** from clause 6.10 to 6.14.

Schedule M of D and C act describe this requirement under 3.2.

USFDA guidelines details about the prevention of microbial contamination under 211.113 Control of microbiological contamination.

MHRA and TGA/PICs describe this requirement under Prevention of Cross-contamination in Production 5.18 to 5.20

#### **In-process testing**

All the guidelines selected for study describe the requirement of in-process testing to confirm that the product is conforming to predetermined specification.

USFDA describes this requirement under 211.110 Sampling and testing of in-process materials and drug products.

Sampling and testing requirements are not detailed under production in MHRA and TGA guidelines whereas the same is detailed under chapter 6 Quality Control.

WHO describe the same requirement under chapter 17 good practices in quality control.

Schedule M of D and C act describe this under 22.4 testing.

### **Calculation of yield**

Yield calculation is essential to understand the loss during production and to take measures to minimize the loss. Calculation of yield is given under 16.4 of WHO guide, 211.103 of USFDA, 5.8 of MHRA and TGA/ PICs. Schedule M of D and C act describe this requirement under section 12.1 documentation; however schedule M does not specify this requirement under production.

### **Packing operations**

WHO describes the packing operations under 16.25 to 16.36.

D and C act describe the packing labeling and storage under different category of dosage forms in the act.

MHRA and TGA/PICs describe packing under section Packaging Operations 5.44 to 5.57.

USFDA details the packing operations under subpart G packing and labeling control.

### RESULTS

### Development of Theory for Production and process control in pharmaceutical industry

Based on the above comparative analysis and discussion on production and process control in pharmaceutical industry as per the different regulatory guidelines below is the theory developed which is common for all the regulatory requirement. Following of the below common theory shall suffice the requirements of all the regulatory guidelines with respect to Production and process control.

#### **Production Area**

The production area shall be designed to allow the production preferably in uni-flow and with logical sequence of operations.

Pipe-work, electrical fittings, ventilation openings and similar service lines shall be designed, fixed and constructed to avoid cross contaminations. Service lines shall preferably be identified by colors and the nature of the supply and direction of the flow shall be marked/indicated.

### Access to production area

Access to production premises should be restricted to authorized personnel.

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### Written procedure

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. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality unit.

Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.

# Equipment

The Equipment used in the production of pharmaceutical products should be of required quality and size. Equipment should not affect the product adversely and it should be designed in such a way that the equipment should be user friendly, safe and cleaning should be easy. Material of construction should not affect the quality of the product.

Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products.

Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation.

All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product shall be properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch.

Major equipment shall be identified by a distinctive identification number or code that shall be recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code.

# Starting and packing materials

The purchase of starting materials is an important operation which should involve staff who have a particular and thorough knowledge of the suppliers and manufacturers.

Starting materials should only be purchased from approved supplier named in the relevant specification and, where possible, directly from the producer. It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the Accepted by venkat

suppliers. It is of benefit that all aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements, as well as complaints and rejection procedures, are discussed with the manufacturer and the supplier.

For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels.

If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.

Starting materials in the storage area should be appropriately labeled. Labels should bear at least the following information:

The designated name of the product and the internal code reference where applicable;

Batch number is given at receipt;

Where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);

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Where appropriate, an expiry date or a date beyond which retesting is necessary.

There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified.

Only starting materials which have been released by the Quality Control Department and which are within their shelf life should be used.

Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labeled containers.

Each dispensed material and its weight or volume should be independently checked and the check recorded.

Materials dispensed for each batch should be kept together and conspicuously labeled as such.

### **Packaging Materials**

The purchase, handling and control of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.

Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorized access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorized personnel following an approved and documented procedure.

Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

Out-dated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

### Weighing and measurement

Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at prespecified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label attached to the instrument.

Components for drug product manufacturing shall be weighed, measured, or subdivided as appropriate. If a component is removed from the original container to another, the new container shall be identified with the following information:

Component name or item code;

Receiving or control number;

Weight or measure in new container;

Batch for which component was dispensed, including its product name, strength, and lot number.

Weighing, measuring, or subdividing operations for components shall be adequately supervised. Each container of component dispensed to manufacturing shall be examined by a second person to assure that:

The component was released by the quality control unit;

The weight or measure is correct as stated in the batch production records;

The containers are properly identified.

Each component shall either be added to the batch by one person and verified by a second person.

### Prevention of cross contamination and Microbial contamination

Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.

Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes.

When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust. Provision should be made for proper air control (e.g. supply and extraction of air of suitable quality).

Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gasses, particles, vapors, sprays or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated.

Among the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, certain hormones, cytotoxic substances, and other highly active materials.

Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses and/or over a long time.

Cross-contamination should be avoided by taking appropriate technical or organizational measures, for example:

Carrying out production in dedicated and self-contained areas (which may be required for products such as penicillins, live vaccines, live bacterial preparations and certain other biologicals);

Conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure;

Providing appropriately designed airlocks, pressure differentials, and air supply and extraction systems;

Minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

Wearing protective clothing where products or materials are handled;

Using cleaning and decontamination procedures of known effectiveness;

Using a "closed system" in production;

Testing for residues;

Using cleanliness status labels on equipment.

Measures to prevent cross-contamination and their effectiveness should be checked periodically according to SOPs.

Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g. for microbiological monitoring and particulate matter where appropriate).

#### Sampling and testing of in-process materials and drug products

To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:

Tablet or capsule weight variation;

Disintegration time;

Adequacy of mixing to assure uniformity and homogeneity;

Dissolution time and rate;

Clarity, completeness, or pH of solutions.

Bioburden testing.

Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications.

In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.

Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

#### **Processing operations**

Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation.

Any necessary in-process controls and environmental controls should be carried out and recorded.

Means should be instituted of indicating failures of equipment or of services (e.g. water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. After use, production equipment should be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.

Time limits for storage of equipment after cleaning and before use should be stated and based on data.

Containers for filling should be cleaned before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

Any significant deviation from the expected yield should be recorded and investigated.

Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes should be sanitized and stored according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at prespecified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label attached to the instrument.

Repair and maintenance operations should not present any hazard to the quality of the products.

#### **Calculation of yield**

Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall either be performed by one person and independently verified by a second person.

#### **Packing operations**



When setting up a program for the packaging operations, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate checklist.

The name and batch number of the product being handled should be displayed at each packaging station or line.

All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.

Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

Normally, filling and sealing should be followed as quickly as possible by labeling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.

The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.

Special care should be taken when using cut labels and when overprinting is carried out offline. Roll-feed labels are normally preferable to cut labels, in helping to avoid mix-ups.

Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

On-line control of the product during packaging should include at least checking the following:

General appearance of the packages;

Whether the packages are complete;

Whether the correct products and packaging materials are used;

Whether any over-printing is correct;

Correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorized personnel. Detailed record should be kept of this operation.

Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock.



### **Finished Products**

Finished products should be held in quarantine until their final release under conditions established by the manufacturer.

The evaluation of finished products and documentation which is necessary before releasing of product for sale should be carried out.

After release, finished products should be stored as usable stock under conditions established by the manufacturer.

### REFERENCES

1. Annex 3 - WHO good manufacturing practices for pharmaceutical products.

- 2. PART 1 Schedule M -Good Manufacturing Practices for Premises and Materials of Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products.
- 3. PART 211— USFDA- Current Good Manufacturing Practice for Finished Pharmaceuticals -e-CFR data is current as of January 12, 2016, Title 21  $\rightarrow$  Chapter I  $\rightarrow$  Subchapter C  $\rightarrow$  Part 211  $\rightarrow$  Subpart B.
- 211.100 Written Procedures and deviations.
- 211.101 Charge in of components
- 211.103 Calculaton of Yield
- 211.105 Equipment Identification
- 211.110 Sampling and testing of in process materials and drug products.
- 211.113 Control of Microbiological contamination.
- 211.115 Reprocessing.
- 4. MHRA -Section II 2EU Guidance on Good Manufacturing Practice (GMP)-Production.
- 5. TGA/PICS describes the Production in CHAPTER 5 Production.

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