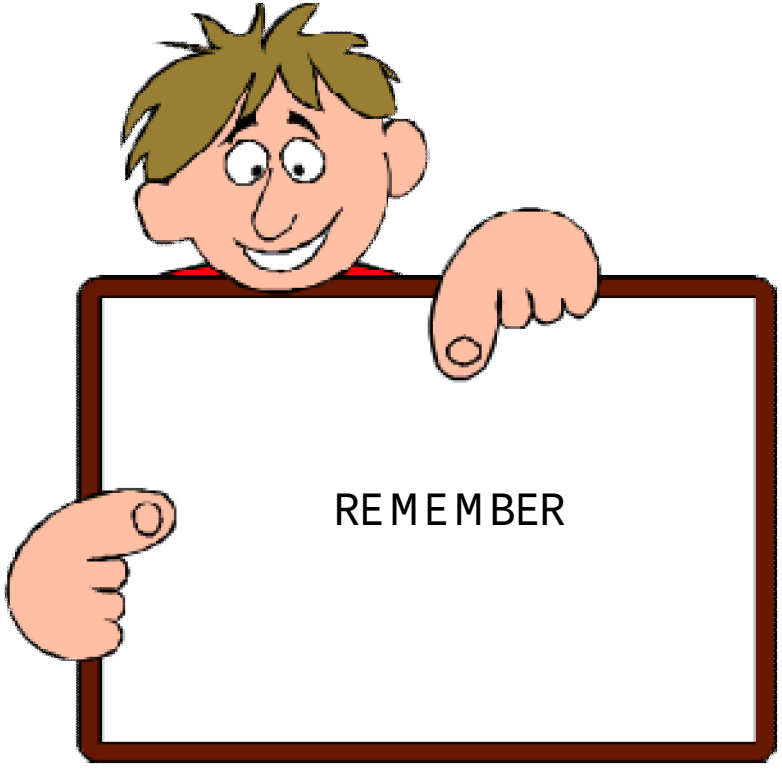
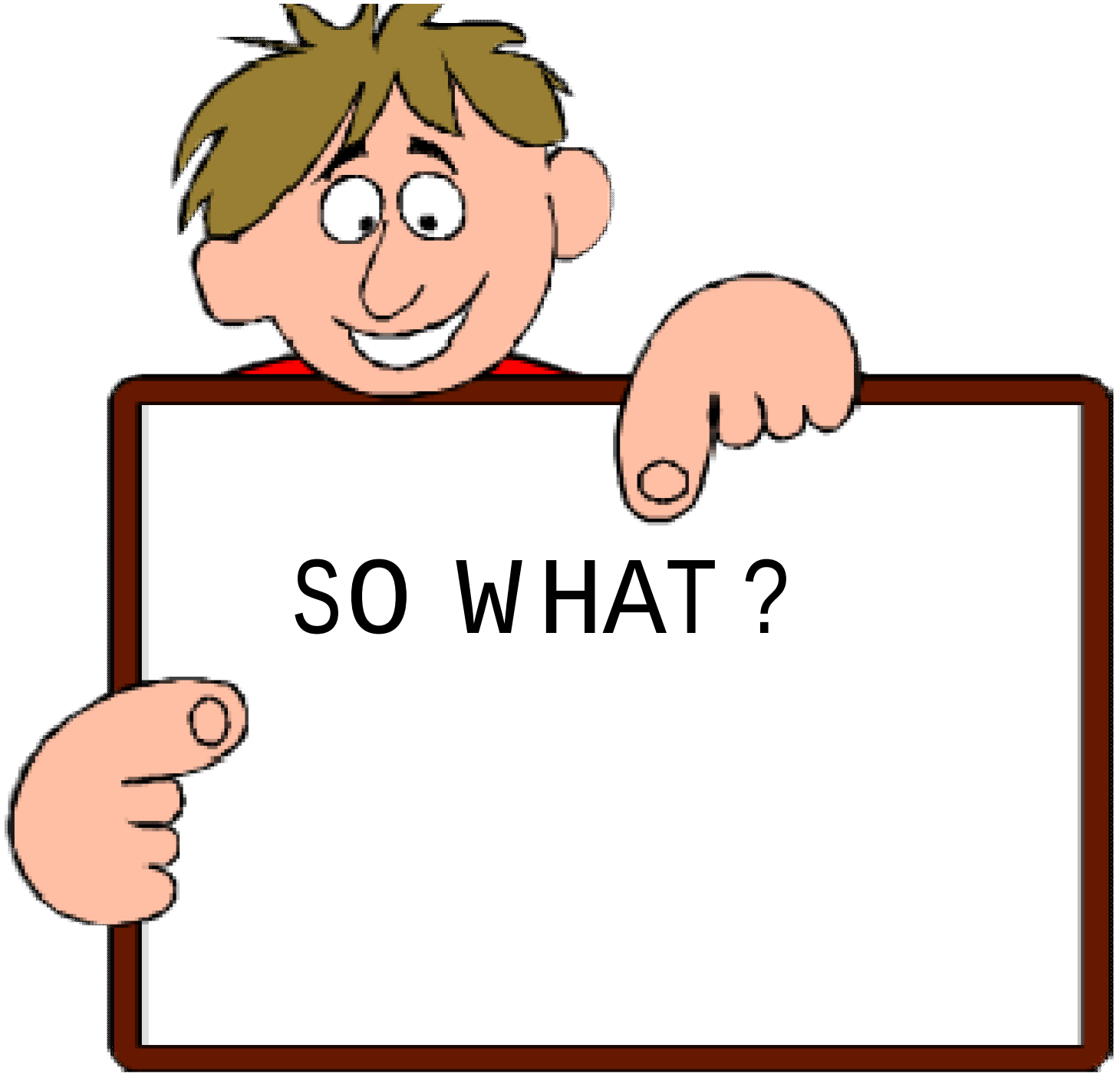
MODULE 7

HVAC AND ASEPTIC PROCESSING

All products and their supporting processes and utilities must be supported by appropriate complete validation.




SO WHAT ?

A good way to start QbD for a new project for an Aseptic process is to start from scratch …….

The recipe is as follows …..

1) Make a group of subject matter experts.
2) List the keywords of your process.
3) For each keyword, implement :
    1) Enablers.
    2) Parameters.
    3) Attributes.
4) Make an assessment : « Direct impact VS Non direct impact »
5) Make a risk assessment.
6) Write a Validation Master Plan

Critical Parameters Process

- Action limits
- Air changes.
- Alert limits.
- As built.
- Aseptic filling.
- Aseptic process
- Air flow
- At rest
- Bio burden
- Cleanroom
- Clean zone
- Contact.
- Contaminant
- Critical processing
- Dosage
- Efficiency

Critical Parameters Process

- Filter
- Gowning
- HEPA
- Isolator
- In operation
- Particle.
- Pre filter
- Core process
- RABs
- Risk based approach
- Room Monitoring system
- Sterile drug substance
- Supplier
- ULPA
- Viable particle
- Sterility

KEYWORD	DEFINITION	CPP	DIRECT IMPACT
STERILITY	MUST COMPLY WITH TEST FOR STERILITY. NO VIABLE PARTICLE DETECTABLE;	C.F.U	YES
CLEAN ZONE	FIVE DIFFERENT ZONES A TO E DEPENDING ON THE DESIGN, AIR FLOW, PRESSURE DIFFERNCE, AND FILTRATION	PRESSURE VELOCITY HEPA RH TEMPERATURE	YES FOR PREPARATION, ASEPTIC FILLING, CRIMPING, OPEN CONTAINER TRANSFERS PREPARATION OF CELL BANKS

Critical Parameters Zones

- Factory
  - Administration.
  - Cafeteria
  - Lockers
  - Canteen
  - Corridors
- Technical
  - Workshops
  - Utiliies rooms
  - Clean steam generation
  - Water treatment
  - HVAC room
  - Corridors

Critical Parameters Zones

- Quality control
  - Sampling area raw materials
  - General labs
  - Microbiological labs
- Warehousing
  - Receiving
  - Dispatching
  - Storage
  - Cool store
  - Tank farm

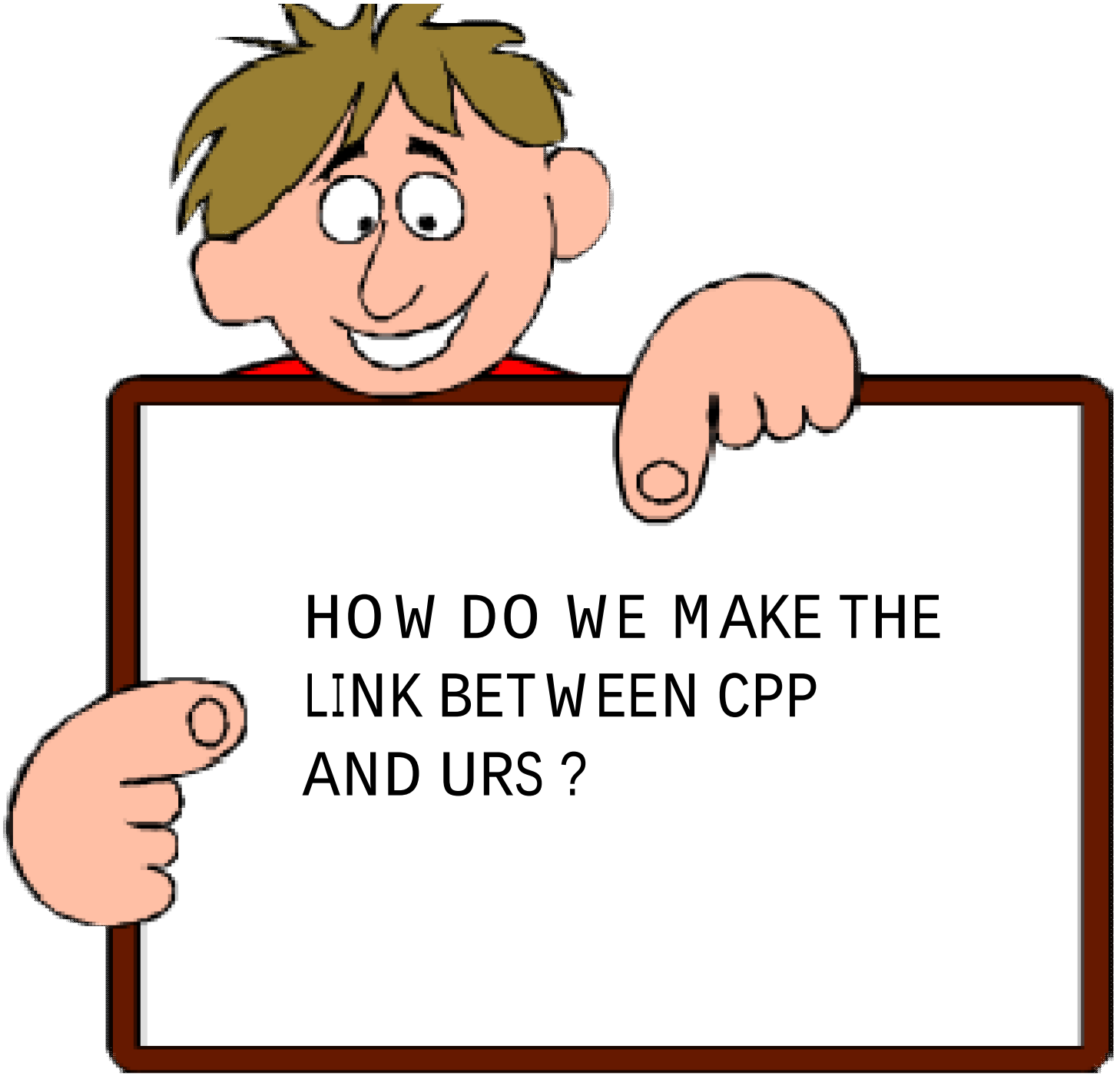
Production Zones

- Corridors
- Airlocks
  - To E
  - To D
  - To C
  - To B
  - Et.c
- Dispensing area
- Sterile filtration area
- Sampling area
- Preparation area
- Production of master cell bank
- Inoculum preparation area.
- Final purification steps area
- Sampling for IPC
- Cell harvesting

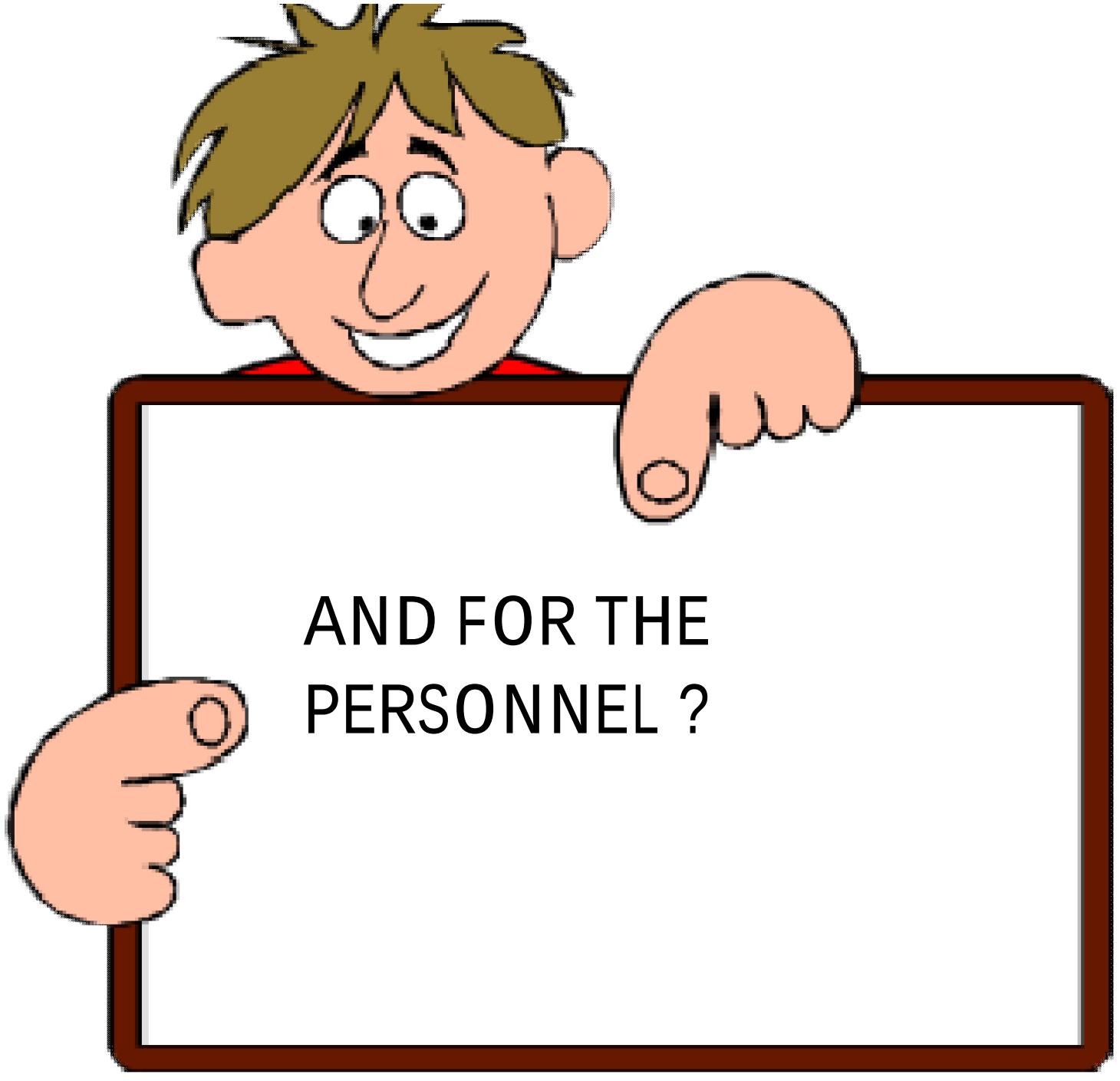
Production Zones

- Virus inoculation.
- Virus deactivation.
- Formulation of buffers
- Final purification
- Final filling
- Container docking
- Washing rooms
- Sterlization tunnel
- Autoclave.
- Crimping
- Inspection

KEYWORD	DEFINITION	CPP	DIRECT IMPACT
HARVEST ZONE	MUST BE IN ZONE 2	CLOSED CONTAINERS. GRADE X TEMPERATURE RH ….	YES
SAMPLING	MUST BE PERFORMED IN AREAS WHICH MINIMIZE THE RISK OF CONTAMINATION	CLOSED GRADE B TEMPERATURE RH ….	YES


HOW DO WE MAKE THE
LINK BETWEEN CPP
AND URS ?

KEYWORD	DEFINITION	URS	RISK
SAMPLING	MUST BE PERFORMED IN AREAS WHICH MINIMIZE THE RISK OF CONTAMINATION	PROVIDE : •PROTECTION AGAINST CONTAMINATION •LOGICAL AND DIRECT FLOW •GOOD STAGING •GOOD ACCESS •NO POSSIBLE CONFUSIONS •NO MIX UPS •MINIMIZE DISTANCES •MINIMIZE HANDLING STEPS	CONTAMINATION FALSE POSITIVES

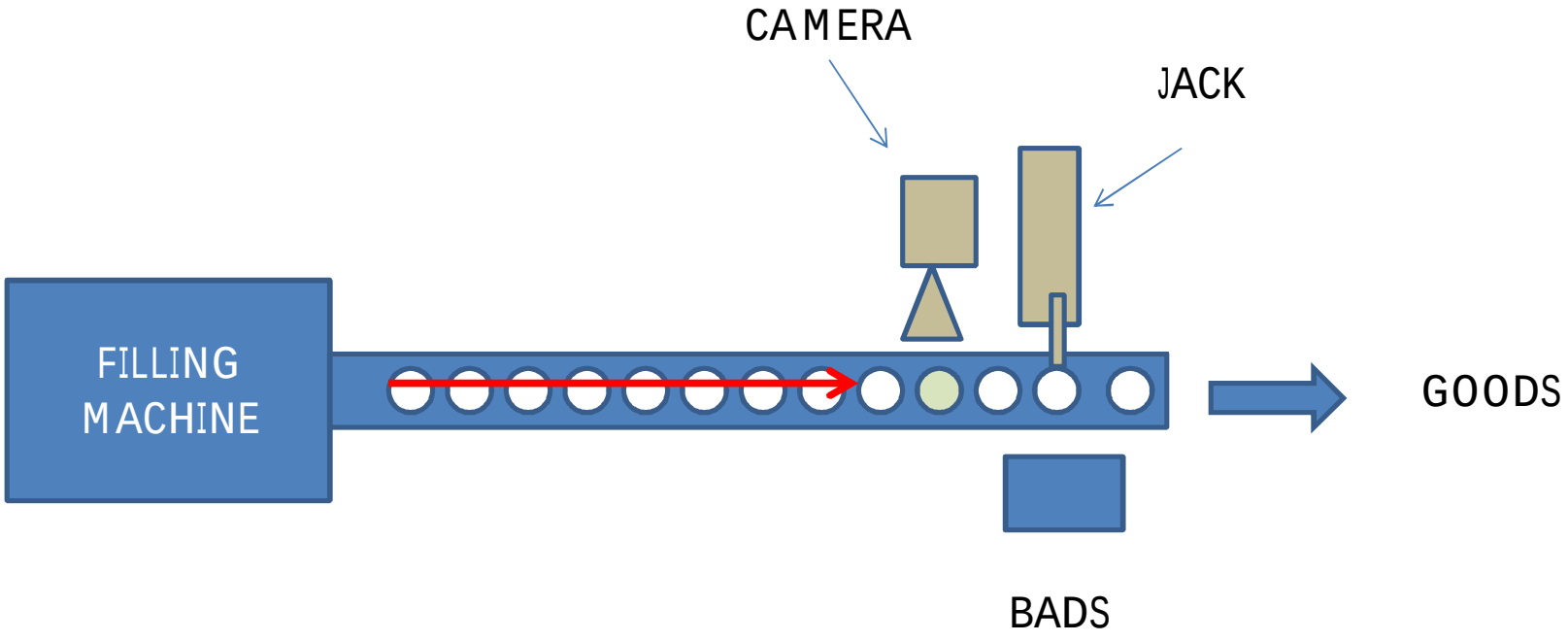

AND FOR THE
PERSONNEL ?

KEYWORD	DEFINITION	URS	RISK
PERSONNEL	MUST BE DESIGNED TO PROTECT THE PRODUCT FROM CONTAMINATION PROTECT THE ENVIRONMENT PROTECT THE PERSONNEL ENSURE SECURITY	SEGREGATION GOWNING DEGAOWNING PROTECTION SECURITY	CONTAMINATION FALSE POSITIVES

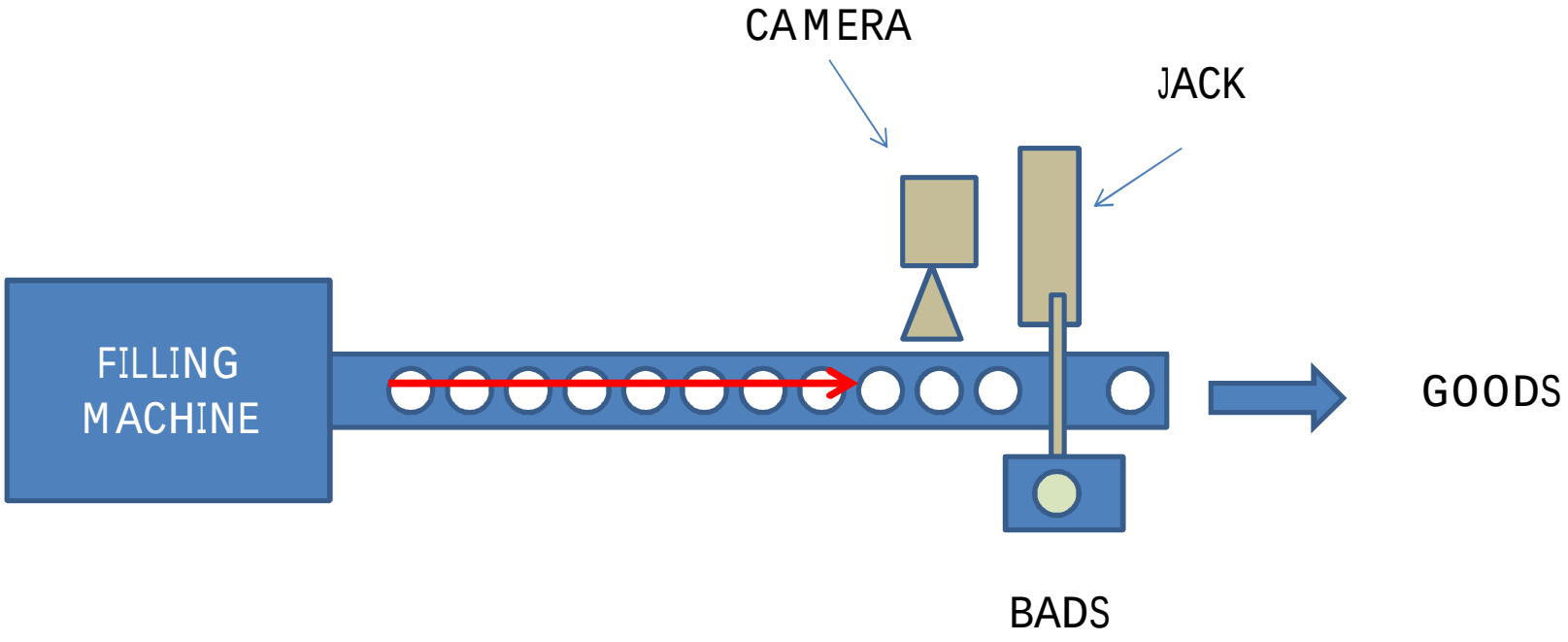
H.V.A.C

PROCESS CRITERIA	EXAMPLE	URS	RISK
CRITICAL ROOM PARAMETERS	TEMPERATURE		
CONTAMINATION	POLLUTED FLOOR	LIST SOURCES OF CONTAMINATION : •EXTERNAL AIR •BAD FILTRATION •DAMAGED FILTERS •BAD AIR FLOW •HVAC FAILURE •PERSONNEL •CONSTRUCTION MATERIALS •DRAINS •SPRINKLERS • MIX UP	EVALUATE CONDITIONS IN CASE OF EQUIPMENT FAILURE RECOVERING TIME INTERLOCKS FAIL SAFE MODES. ….
NOT AFFECTED	CLOSED SYSTEMS		


ARE YOUR FAMILIAR
WITH FAIL SAFE ?



A CAMERA INSPECTION STATION DETECTS BAD VIALS AND SENDS A SIGNAL TO AN EJECTION STATION



THE BAD VIAL IS SENT TO A REJECTED CONTAINER


SO HOW CAN I BE FAIL
SAFE FOR HVAC ?

IT IS SOMETIMES POSSIBLE :

1. LOCKERS : SIGNAL TO HVAC
2. COOLING BATTERIES
3. ETC

IT IS SOMETIMES NOT POSSIBLE :

1. OPERATOR ACTION IN CASE OF FAILURE

IN DESIGNING THE CRITERIA AND THE CPP CONSIDERATION MUST FOCUS ON RISK AND OPERATING RANGE.

THIS WILL LEAD THE TIGHTNESS OF CONTROL RANGE OF THESE PARAMETERS

H.V.A.C

IS TEMPERATURE A CRITICAL PARAMETER ?

YES IF THE CRITICAL QUALITY ATTRIBUTES LIKE

- QUALITY
- STABILITY
- EFFICIENCY

ARE AFFECTED

→ CRITICAL PARAMETER → QUALIFICATION

H.V.A.C

IS TEMPERATURE A CRITICAL PARAMETER ?

NO IF THE CRITICAL QUALITY ATTRIBUTES LIKE

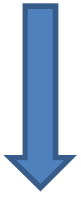
- QUALITY
- STABILITY
- EFFICIENCY

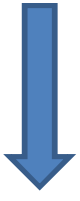
ARE NOT AFFECTED

→ GENERAL PARAMETER → COMMISSIONING

H.V.A.C – TEMPERATURE

GRADE	GENERAL PARAMETER	CRITICAL PARAMETER
A – ISO 5	18 – 26 °c	MORE RESTRICTIVE
B – ISO 7	IDEM	MORE RESTRICTIVE
C – ISO 8	IDEM	MORE RESTRICTIVE
D – ISO 8	17 – 27	MORE RESTRICTIVE
E - NA	12 - 28	MORE RESTRICTIVE





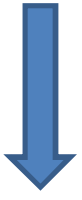
COMMISSIONING

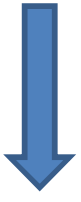
QUALIFICATION


SO WE CAN DO THE
SAME FOR ALL THE CPP

H.V.A.C – RELATIVE HUMIDITY

RH	GENERAL PARAMETER	CRITICAL PARAMETER
CONTACT WITH PRODUCT	NO	YES HUMIFIFIER MUST HAVE THE SAME CPP AS WATER USED IN THE PROCESS
	NO	YES DESSICANT MUST BE EVALUATED AS CPP



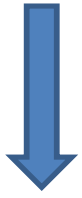


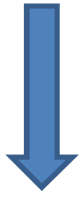
COMMISSIONING

QUALIFICATION

H.V.A.C – PARTICLES

PARTICLES	GENERAL PARAMETER	CRITICAL PARAMETER
CONTACT WITH PRODUCT	NA	YES
	NA	YES

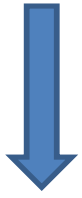


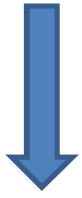


COMMISSIONING QUALIFICATION

H.V.A.C – MICRO ORGANISM

MICRO ORGANISM	GENERAL PARAMETER	CRITICAL PARAMETER
CONTACT WITH PRODUCT	NA	YES
	NA	YES



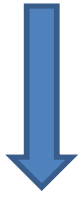


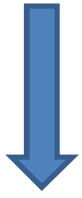
COMMISSIONING

QUALIFICATION

H.V.A.C – ROOM AIR CHANGE RATES

ACH/HR	GENERAL PARAMETER	CRITICAL PARAMETER
CONTACT WITH PRODUCT	NA	YES
	NA	YES





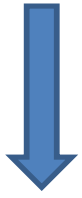
COMMISSIONING QUALIFICATION

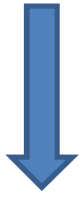
IMPACT ON COSTS :

-BATTERIES SIZES
-AIR HANDLING UNITS SIZES
-ENERGY CONSUMPTION
-NUMBER OF FILTERS
-……

H.V.A.C – RECIRCULATION

ACH/HR	GENERAL PARAMETER	CRITICAL PARAMETER
CONTACT WITH PRODUCT	RISK ASSESSMENT	RISK ASSESMENT





COMMISSIONING QUALIFICATION

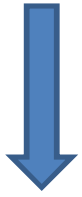
RISK OF CROSS CONTAMINATION

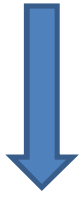
POTENT PRODUCTS

MULTI PRODUCTS

H.V.A.C – RELATIVE PRESSURE DIFFERENCE - CASCADES

DELTA P	GENERAL PARAMETER	CRITICAL PARAMETER
CONTACT WITH PRODUCT	RISK ASSESSMENT	RISK ASSESMENT





COMMISSIONING

QUALIFICATION

EVALUATE :

1. OPEN OR CLOSED SYSTEMS
2. LOCAL EXHAUSTE : HOODS, DEDUSTERS
3. AIRFLOWS
4. POWDERS
5. REVERSAL FLOWS

MONITORING

PARAMETER	CRITICAL	MONITORING
PARTICLES	YES	ON LINE CONTINUOUS MONITORING RECORDING DATA INTEGRITY
ROOM AIR SUPPLY	YES	DEFINE WHICH ROOMS CAN BE SUPPLIED WITH FROM THE SAME AHU DEFINE RECIRCULATION AND % OF RECIRCULATION
GEOMETRY	YES	ESTIMATE USER LOCATIONS ESTIMATE WORST LOCATION IN TERM OF AIRFLOW AND PARTICLES ….

Start with the end in mind : start with the corrective actions

User requirements : H V A C :

1. Perform investigation for possible source of contamination.
2. Perform air flow patterns.
3. Perform smoke tests.
4. Review aseptic technics of personnel.
5. Review gowning requirements.
6. Inspect incoming airfilters for leaks in filter.
7. Review air pressure differential across filter.

Start with the end in mind : start with the corrective actions

User requirements : H V A C :

1. Review room desinfection/sanitation SOPs
2. Review sanitation intervals.
3. Review sanitation efficiency.
4. Check area pressure differential.
5. Evaluate equipment as source of contamination.
6. Evaluate integrity of the room (peeling paints, cracks ..)
7. Review risk to product.
8. Review maintenance and access

ONCE YOU HAVE DONE ALL THAT.

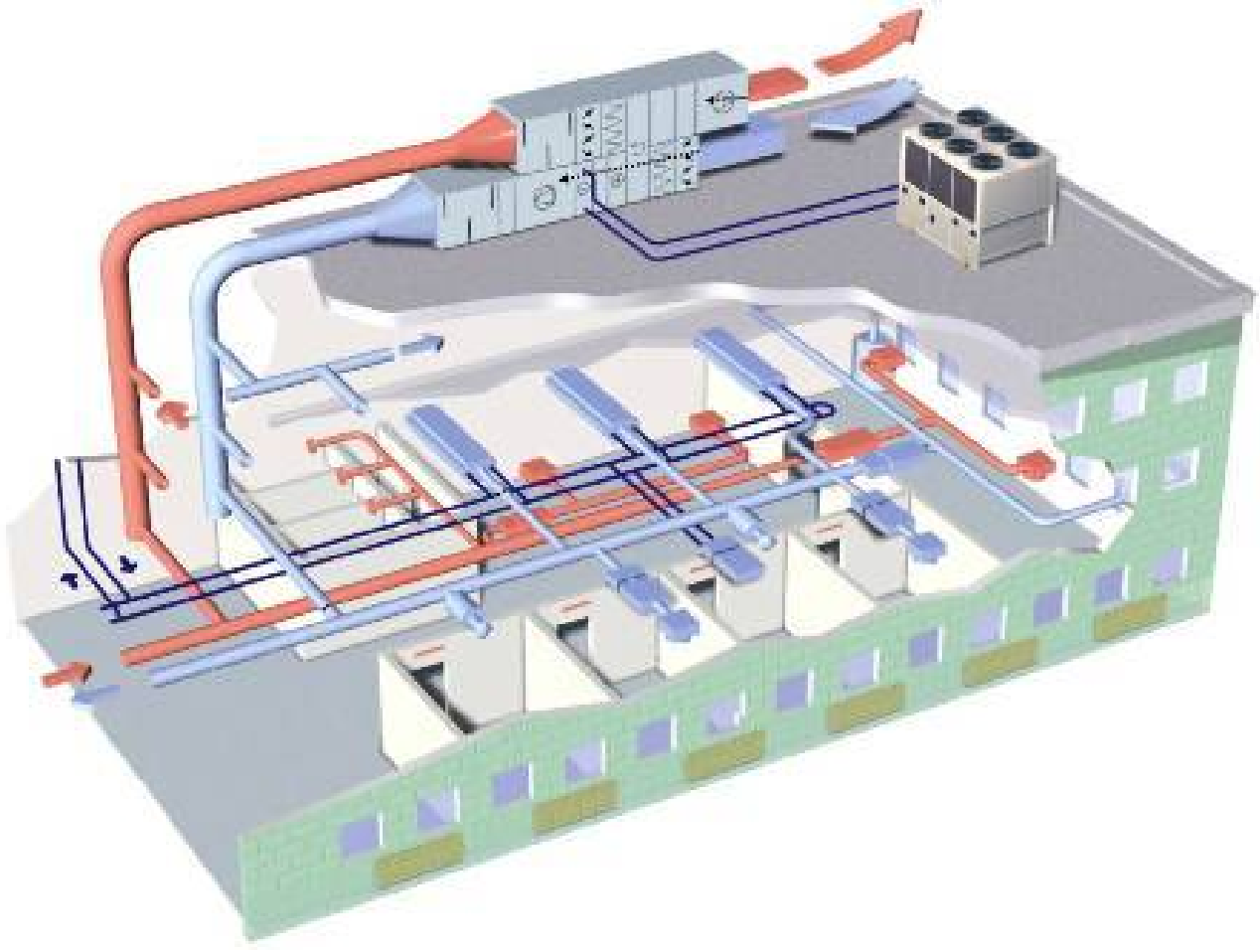
ENGINEERS WILL WRITE THE SPECIFICATIONS

THEIR DESING WILL BE BASED ON YOUR URS AND WILL FEED THE QdB AND THE RISK ASSESSMENT

YOU WILL BE INVOLVED IN THESE Activités

THEN QUALIFICATION WILL START

YOU CAN GET THAT



DEPENDING ON HOW GOOD THE COMMUNICATION IS

OR THAT !!!!!!!!