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APPLYING GMP TO COMPUTERIZATION IN A SOLID-ORAL-DOSAGE-FORM-FACTORY

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ABSTRACTS

Quality Assurance and Pharmaceutical security as well must be given a particular consideration both for hardware and software when computerized pharmaceutical industrial operations are concerned.

Hardware: The preparation of validation should begin with the design of a computerized system and rely upon specifications and upon defined operational limits.

It is suitable to prepare documentation as from the development of the system in order to obtain a fruitful communication between all those concerned with design, implementation, maintenance, validation and auditing.

A revalidation procedure should be prepared and maintained updated, in the event of a change in one or several operating conditions.

Software:As with hardware, validation of software should be envisioned as early as the development phase. Preparation of test procedures and documentation should start at this very stage. Qualification and validation will be designed to find errors in the program and not to prove that no errors exist. They will be carried

out at the operational boundaries of the software and will aim at testing the critical decision paths of the program. Verifications must be repeated a sufficient number of times to demonstrate that the results are repeatable.

As with other pharmaceutical manufacturing systems, a formal procedure should exist to support changes made to the software. Vendor supplied software should be verified and documented with the same rigour and details that in-house developed software. Manual back-up systems must be provided for and regularly tested in the event of failure of the automated process. Computerized systems and good manufacturing practices applied to manufacturing of solid oral dosage forms: An application of the above-stated principles is given and illustrated.

Principle

In 1962, NASA launched Mariner 1 on a mission to Venus. The rocket veered of course and had to be destroyed. The investigation conducted afterwards showed that the reason for it was located inside the software of the rocket computer: one single hyphen had been omitted from one the program statements and it costed NASA 18$. million.

Another tragic accident did occur in 1986 : two persons died and another one was seriously injured due to a problem in the computer software which controlled a radiation therapy device. Normally the operator would enter instructions into the computer corresponding to the type of radiation (X-ray or electron beam), their intensity and so on ...

The operator could modify the settings after they had been entered in case of change in parameters or in case of error. The investigation, made after the accidents revealed the software did correctly accept changes concerning the type of radiation but not those concerning their intensity if the changes were made within a period of time of eight seconds following the original entry.

These examples demonstrate, if need be, that hazards and risks due to computer systems do exist and the necessity to know,validate and control them in a comprehensive manner.

Computerized systems used in the pharmaceutical industry must, as a matter of fact :

. guarantee pharmaceutical security,

. assure coherence between all data.

To obtain that :

. they must be validated,

. be subject to regular controlling and auditing.

Validations and audits must be concerned with both hardware and software, not only separately but also as a direct function of them being interrelated.

Hardware

Specifications and operational limits

No serious validation can be made if precise and documented specifications and operational limits have not been defined. This step is necessary to define hardware suited for its intended function and to ensure that it will not be affected adversely by environmental conditions such as humidity, temperature, electrical and electromagnetic harmfull effects. The configuration of the system should be completely described including the interfaces, that is to say the way components of the system communicate together.

Qualification

Qualification procedures should allow to check that the hardware system meetsits specifications and will operate reliably within the defined environment. These procedures should test the hardware at the limits under which it will have to operate. It does not imply to test at the outer limits where the hardware does not operate correctly. They should instead of that, be performed with the parameters overstepping operational limits defined in the specifications,

limits within which the system must operate without risks and beyond which the system would be in an out-of-control state.

Documentation

It is necessary that a system be fully documented from the beginning of its development and not afterwards when the system is already operating. This documentation should have for purpose to allow proper communication among those who have developped the system, those who make it work, those who maintain it, those who have to make changes, those who have to validate and to audit the system. Everybody should be able to know what has been done, how and why it has been done.

Revalidation

The hardware system which has been validated under a set of defined conditions, should be revalidated if one of these conditions has changed. Any change should be evaluated in order to determine its possible effects on the system. For this reason, a documented program of revalidation should be established and kept updated in order to be able to follow changes and determine critical points that must entail revalidation.

Software

Although validation of computer software seems to be more complicated that for hardware, the purpose and principle of validation do apply in the same way in both cases. The purpose in all cases, is to demonstrate that a program performs effectively the intended functions and does it accurately and reliably. The validation of a system should not intervene only when the system starts running : the appraisal of qualities and defects could not at this time, be extensive enough. Validation should therefore begin with developing of the system.

Development

Specifications, at this stage, must be sufficiently detailed to allow communication of the software requirements to the team in

charge of design and implementation of the system. Communication should be complete enough to allow for the objective verification that requirements have been met.

During the stage of development, it is also necessary to start preparation of testing protocols and documentation.

The probability that all critical steps of the program be verified is relatively higher when procedures for checking have been defined during the development phase of the system.

Testing and validation

Once more, it is to be noted that the definition of checking procedures should begin with the decision of computerising the system. Both procedures should be developed in parallel, checking being able to start during the development phase.

Checking procedure should be conducted in order to find errors in the program and not to prove that such errors do not exist. For computer software, a test can be considered as successfull when it allows to expose errors that had not been anticipated.

The program of verification should explore boundary limits of the software (it is the worst case procedure), to be fully significant. For that, it is necessary to introduce data slightly above and below operational limits. These boundary conditions are important to consider as most errors do occur around limits.

Verifications made at these points should equally comprise testing to evaluate the way the system reacts to entry of unforeseen data : for example alphabetic data when numeric data should be given; or the entry of more characters than the program has been designed to accept.

Finally the software system should be verified after it has been integrated to the computer system. Such verifications do apply both for hardware and software. That one given component can respond accurately on the individual level, does not necessarily mean that this component will still work correctly when interfaced with other components.

It is not rare to find components that work correctly on the individual level but not when gathered together with other it has to be reminded that automated systems must give birth to consistent results during their work. It means that a specific set of data input must always give birth to a specific set of data output.

Performance of a single run of checkings is not sufficient to ensure that the program works correctly. Checkings should be repeated a sufficient number of times to demonstrate that the results are repeatable.

Maintenance

The term maintenance applies to correction of errors or abnormalities in the program or to enhance or adapt a program in order to make it more suitable to the evoluation of needs. As with other systems used in pharmaceutical manufacturing, a documented procedure is necessary to control changes.

Documentation

At all stages from design to implementation and maintenance, validation procedures should be taken into account during the whole life of a computer system. This documentation should be permanently updated.

It is only complete, clear and updated documentation that will allow proving that a computer system is under control.

Poor documentation is at best confusing and at worst misleading. It has not to be voluminous, but must be easy to understand and to use.

The user's manual is an essential part of software system. It should correspond to the actual version of the system.

It should comprise all relevant instructions to allow succesfull performing of the program; these instructions comprise description of correct inputs, expected outputs, available program options and error messages as well as corresponding corrective measures.

Revalidation

As with hardware, a documented procedure should exist to allow revalidation of software. As documentation is an integral part of software systems, it should correspond to the actual software version and not to its past or future characteristics.

Vendor-supplied software

It is impossible to validate a software systems when you cannot understand correctly what actions the program is performing.

Using a vendor can relieve you from part or all of designing of a system, but it will not relieve you from the responsibility to ensure that the system works correctly and reliably, in the same way as it is with a sterilisation oven where you cannot be relieved from validating sterilisation cycles.

The pharmaceutical manufacturer should establish development and performance standards according to which programs and documentation given by the vendor would be checked, in the same manner as it would have been, had the system been developed in-house.

Validation of the software should be documented, even if part or all of it has been done by the vendor. The fact that the vendor certifies he has performed validation cannot be considered as sufficient.

Manual back-up systems

It is necessary to have pre-established procedures, well documented and validated in case of failure of the system. Operators should know what they have to do in case of failure. They should be able to determine at what step of the process the failure has occured and have detailed information on what they should do.

Training of operators should be periodically made, due to the fact that failures are generally rare, giving them very few opportunities to practice.

Points to consider in the process

Manual back-up systems

Functions controlled by a computer system can generally be controlled by a manual back-up system.

It is necessary to give particular attention to the controls of the process and to determine interaction between manual and computerized process controls and to define how manual intervention can by-pass or up-grade the computerized process.

Standard operating procedures should describe what is authorized, who can do it, how and in what circumstances and how these data are documented. The system should be designed so that it can detect and react to manual interventions and register them.

Control of inputs and outputs

Controls should allow for checking that inputs and outputs are effectively accurate. To check the degree and nature of controls and use.

Treatment of errors is an important problem : procedures for treatment of errors should be established.

Documentation on the process

Most systems can provide detailed documentation on the process. The question is to know if the documentation brings effectively all necessary information; for example, a batch record made by a computer: determine if all necessary information is obtained.

Monitoring of computerized operations

What is effectively realised should be checked against what the computer states, for example :

- read the effective temperature and check what the computer states,
- check that a product meant to be quarantined effectively is,
- is treatment of batch tails when they are incorporated into the next batch, taken into account in the manufacturing formula. (the same for reprocessing).

- check the tare of empty containers,
- check physically the emptiness of a container, or take for basis its theoretical tare, if no part of the container has ever been changed,
- check all the balances, whatever their weighing range is as well as regards their accuracy in absolute value as their sensitivity towards variations. Check that the weighing ticket wears the same information as the screen,
- check that bar coding reflect accurately the relevant data, that reading with a laser beam pencil of this bar code brings about the accurate data.

QUALITY ASSURANCE IN MANUFACTURING OF SOLID ORAL DOSAGE FORMS : COMPUTER SECURITY

The steps of the manufacturing process as used by Roussel-Uclaf

At the top, on the right of the table, see major raw materials coming in, packed in "big bags". Each raw material has its own feeding system working by gravity and going down into an automated weighing system. For checking of the raw material being the one expected, a control system does exist : on the upper floor the big bag label is read by a laser beam pencil and the information transmitted to the central processing unit. When data are correct, the system allows the loading of the container, at the lower level. (see point 3).

For small an medium quantities of raw materials, weighing is performed manually (see points 3 and 4). Balances are connected to the computer. The laser beam pencil reads both the identity and the batch number of the raw material. The acceptance/rejection of the batch by quality control is put into the system so that if the identified batch has been rejected, the information "system blocked" appears on the screen and the raw material cannot be used. If the raw material has been accepted, it is incorporated to other components and blended; the mix is submitted to wet granulation, passed

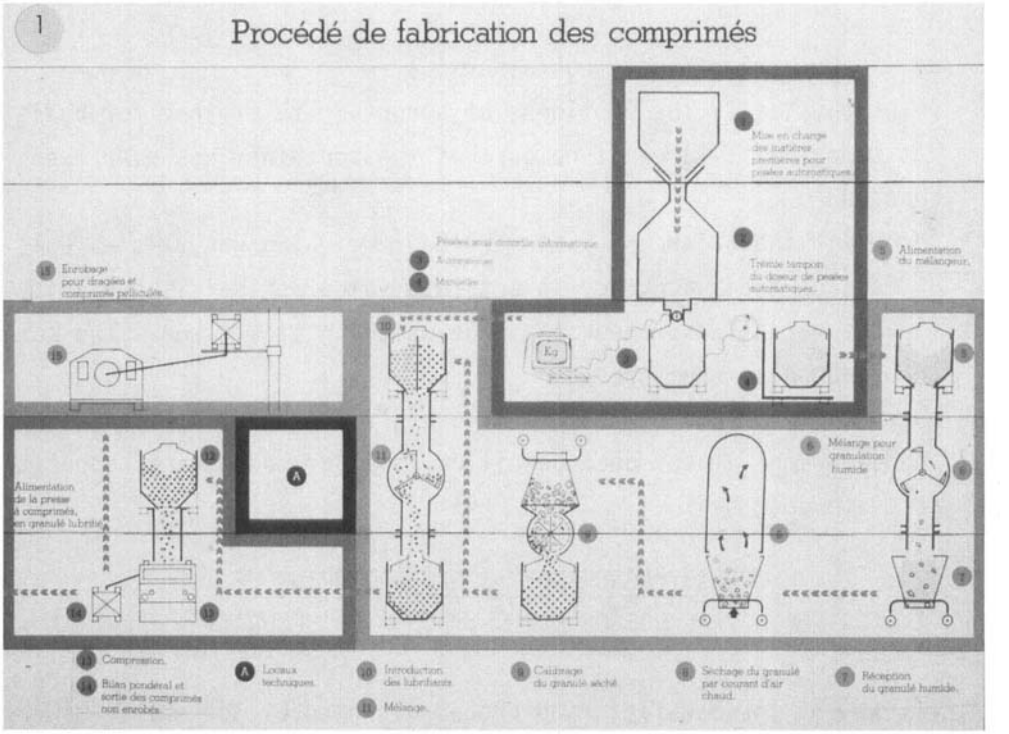

Figure 1. Scheme of the process

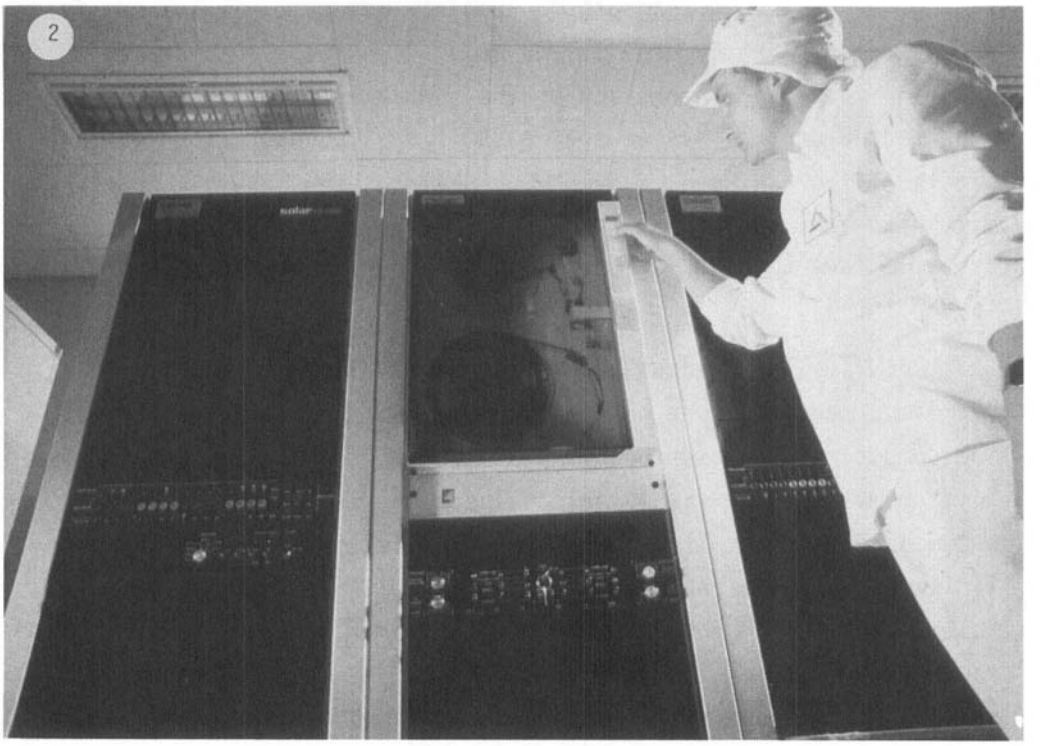

Figure 2. The solar computer

Figure 3. Printer

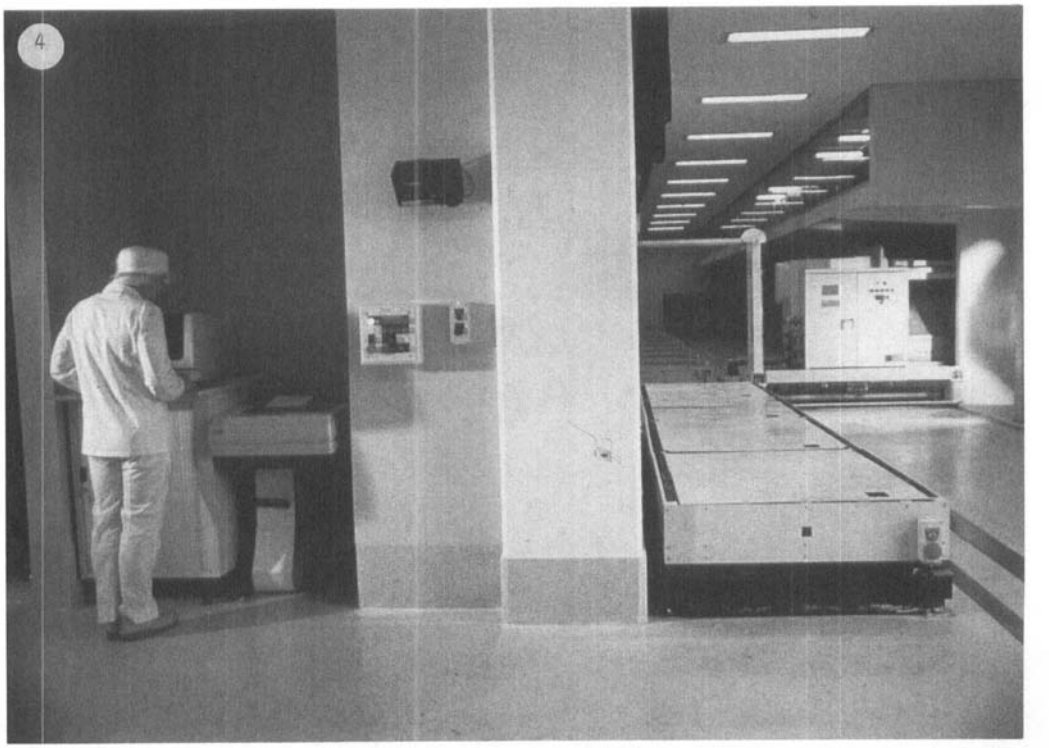

Figure 4. Automatic weighing

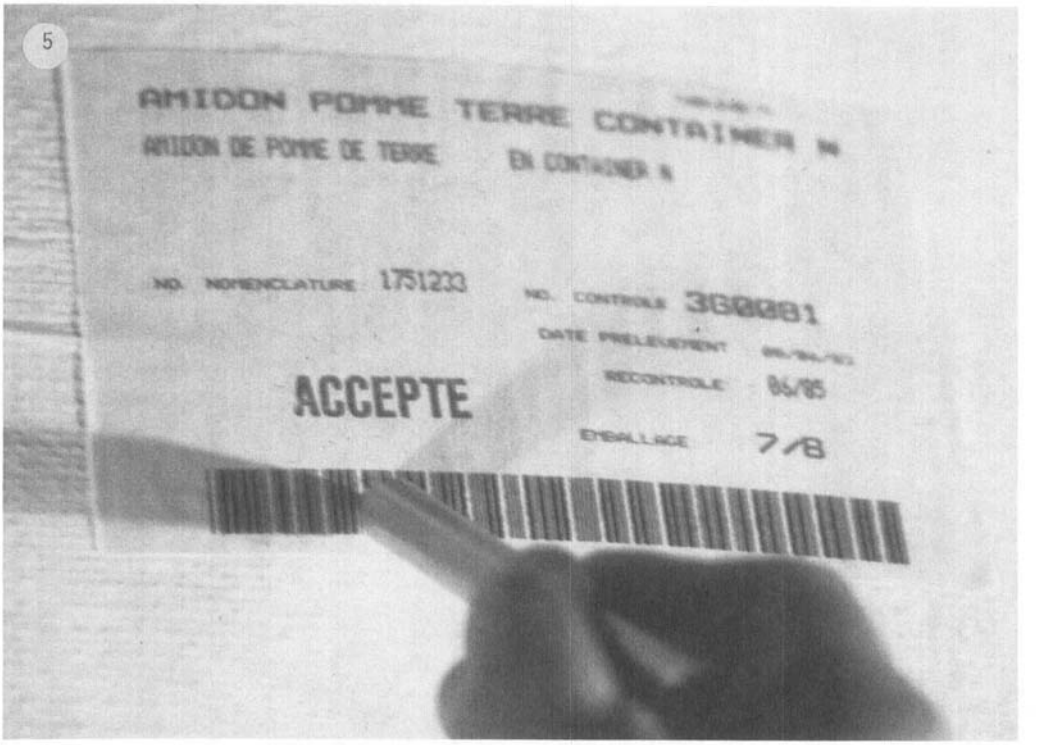

Figure 5. Bar code reading on a big bag

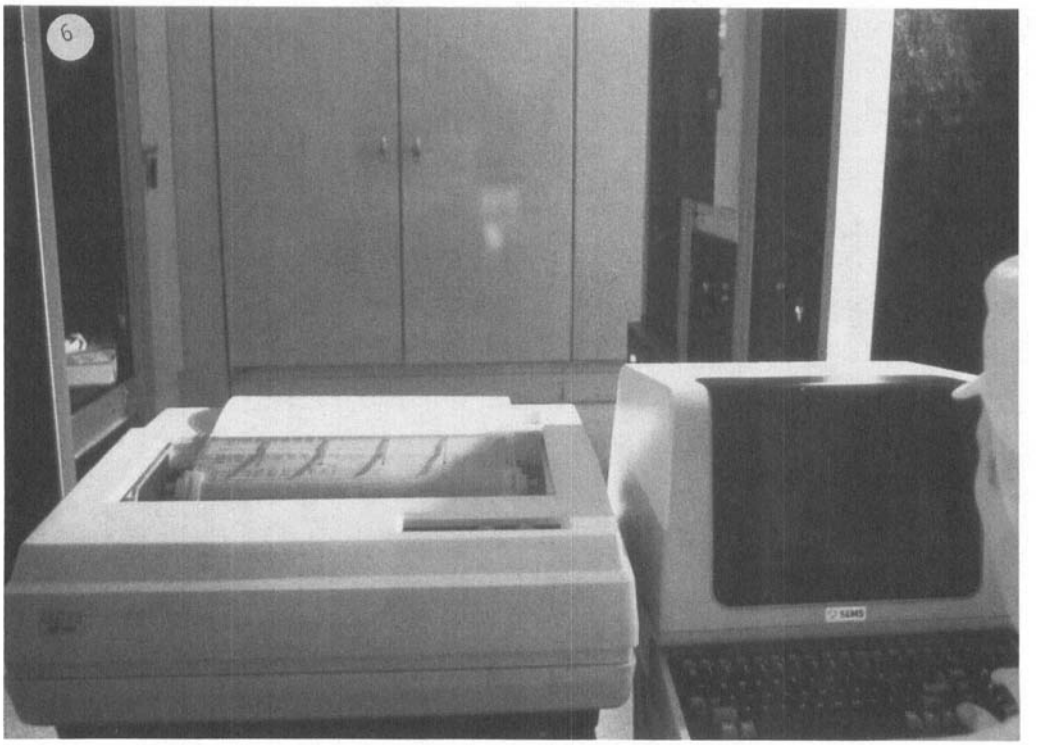

Figure 6. Launching of manufacturing phases

Figure 7. Manual weighing workshop

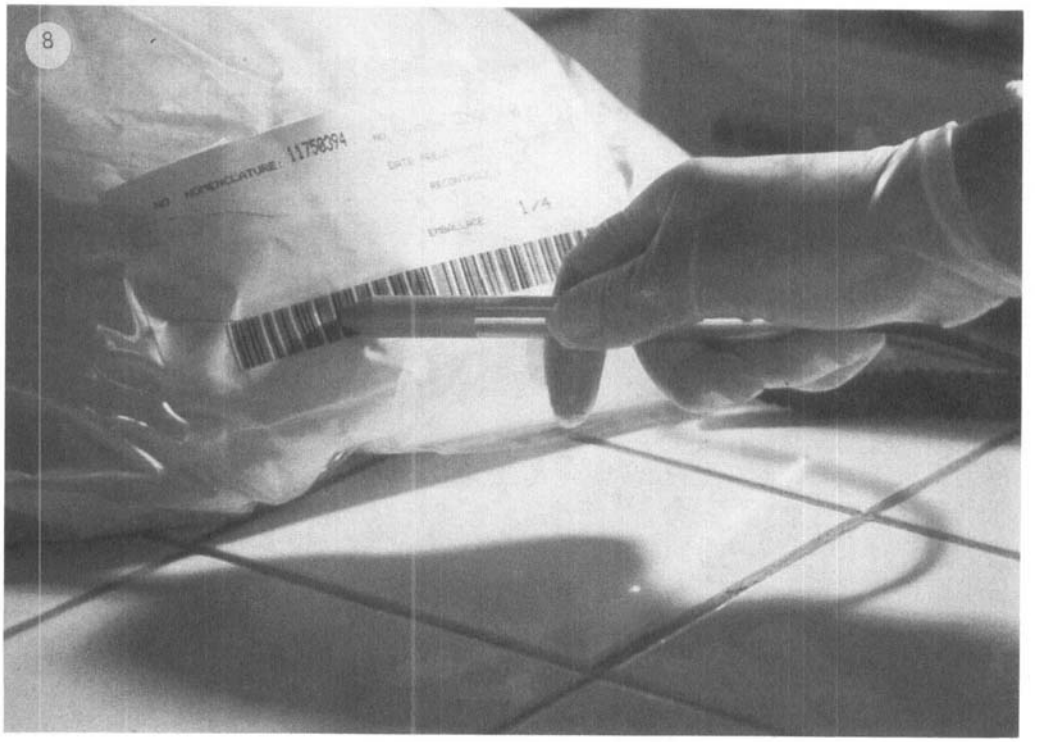

Figure 8. Manual Weighing

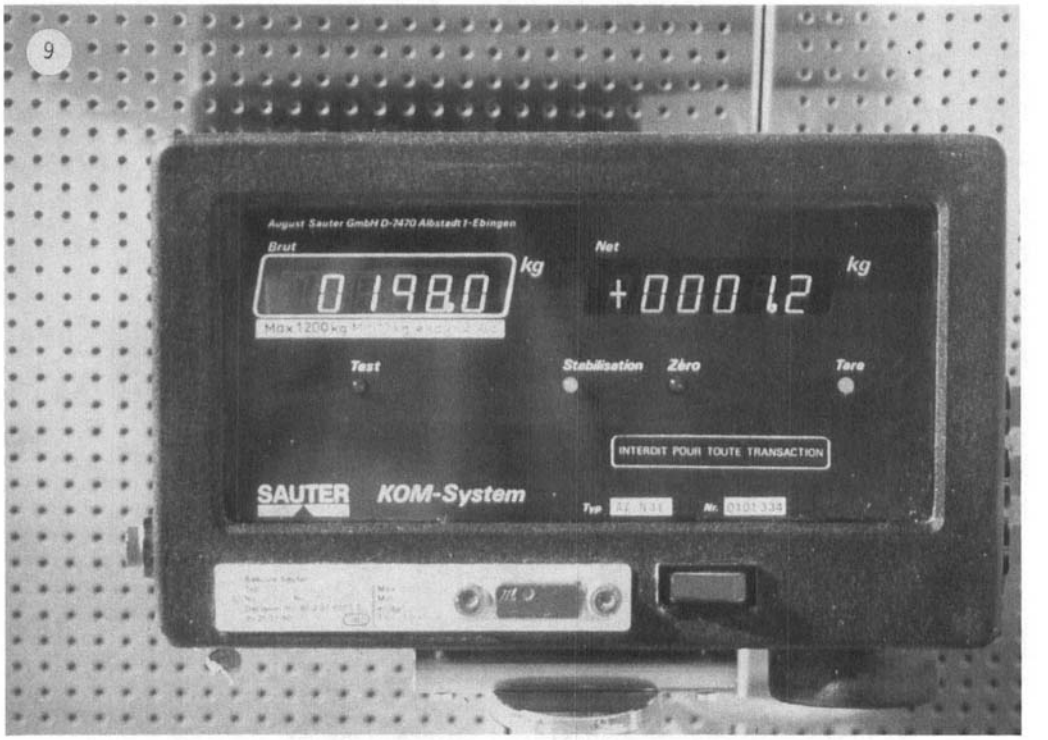

Figure 9. Screenfor following of weighing for large containers

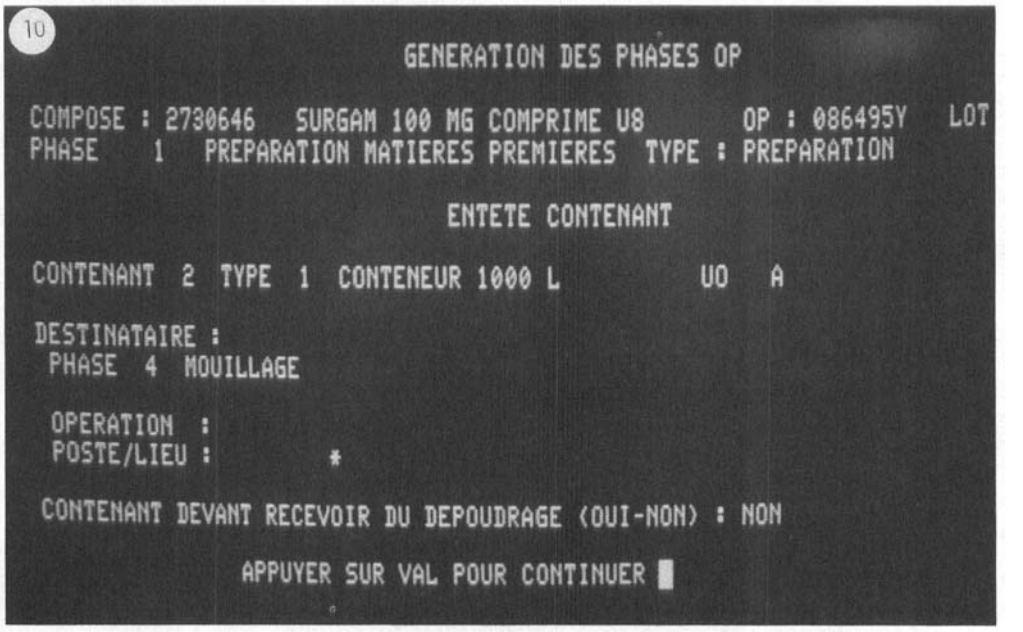

Figure 10.Control screen : manual weighing

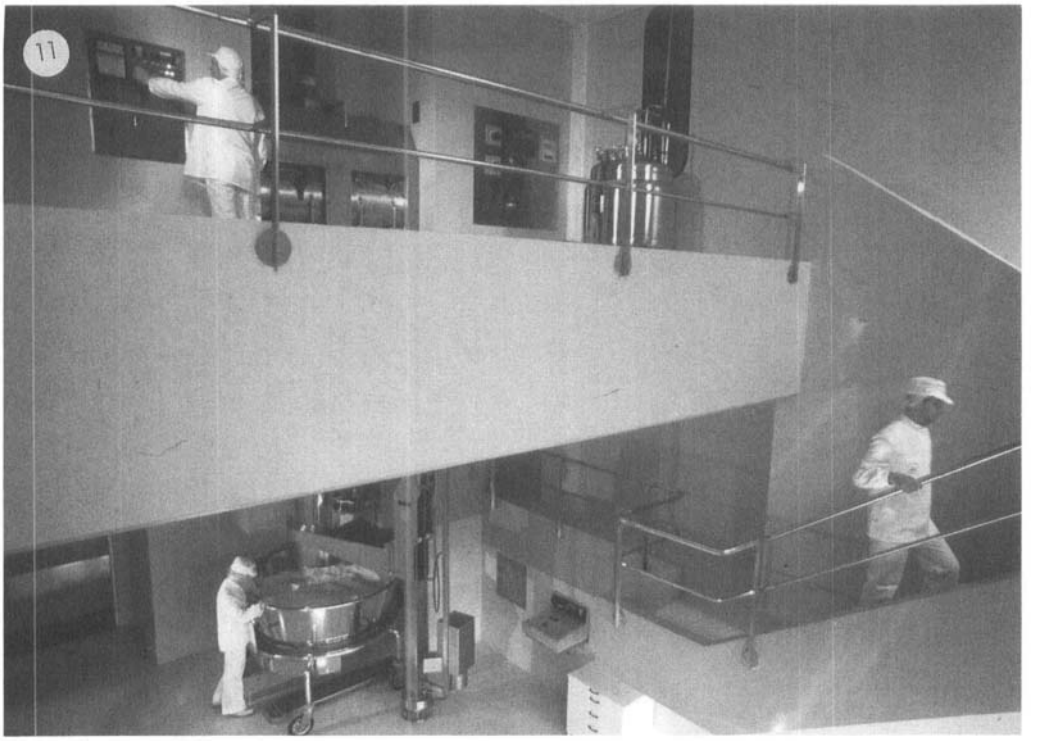

Figure 11.3000 liters blender

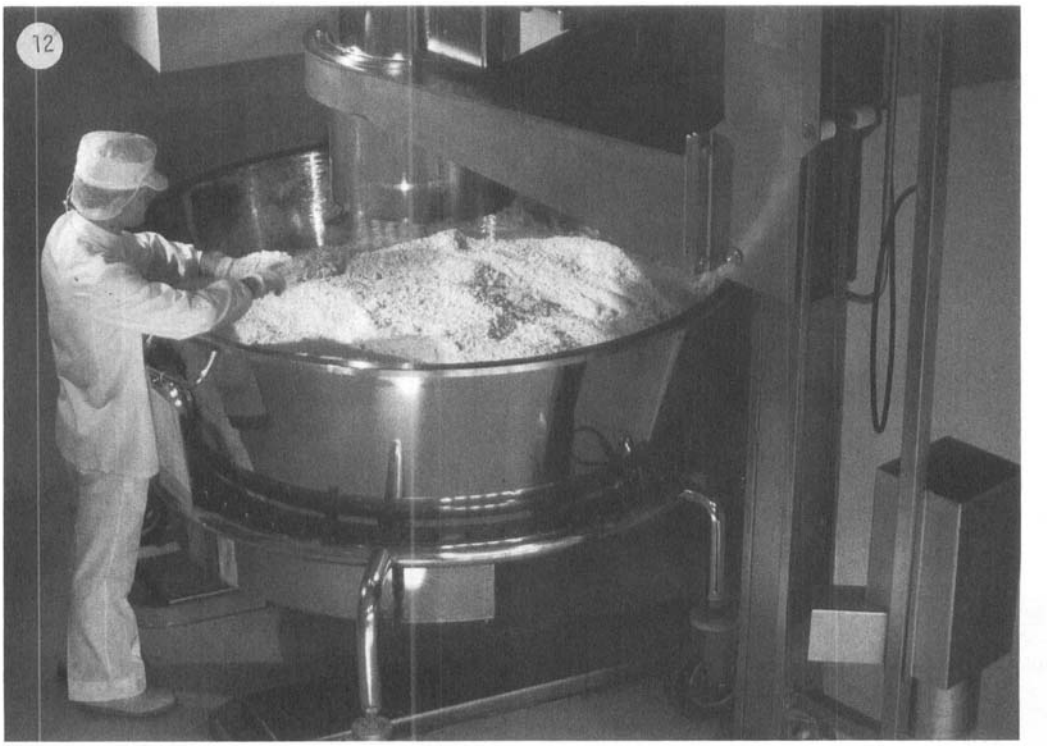

Figure 12.Alexanderwerk sieve

Figure 13.Aeromatic 18 flow bed drier

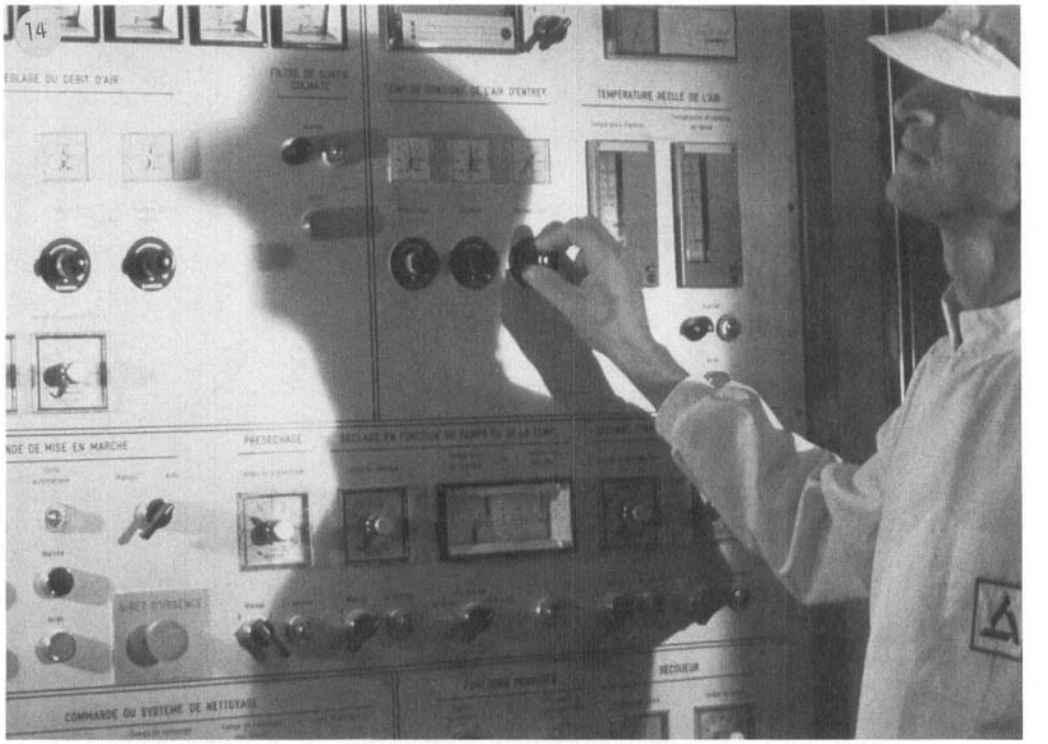

Figure 14.Details of working board of aeromatic

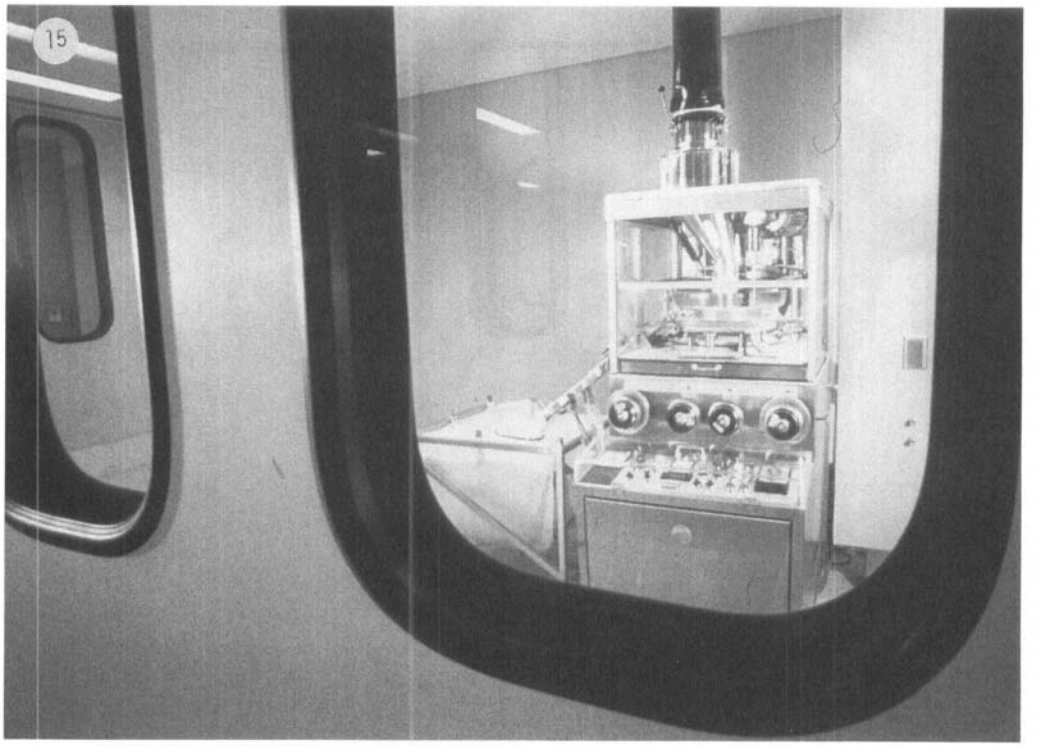

Figure 15.Box for tabletting machine Killian RX

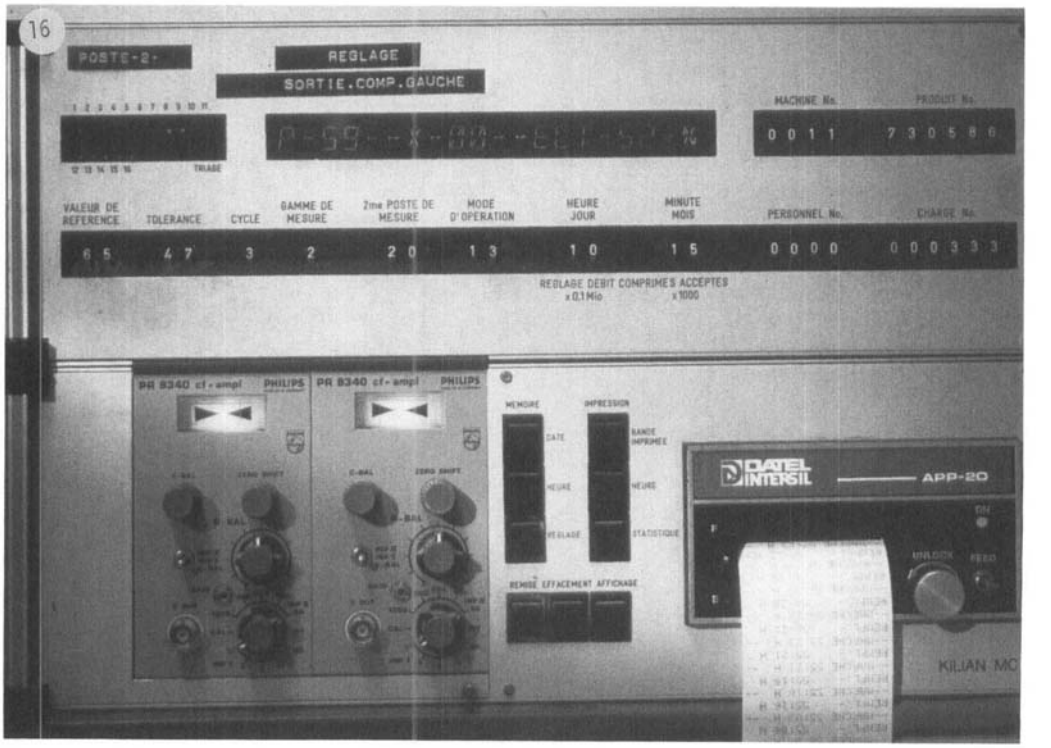

Figure 16.Microcomputer of the Killian

Figure 17.Working board of the Killian

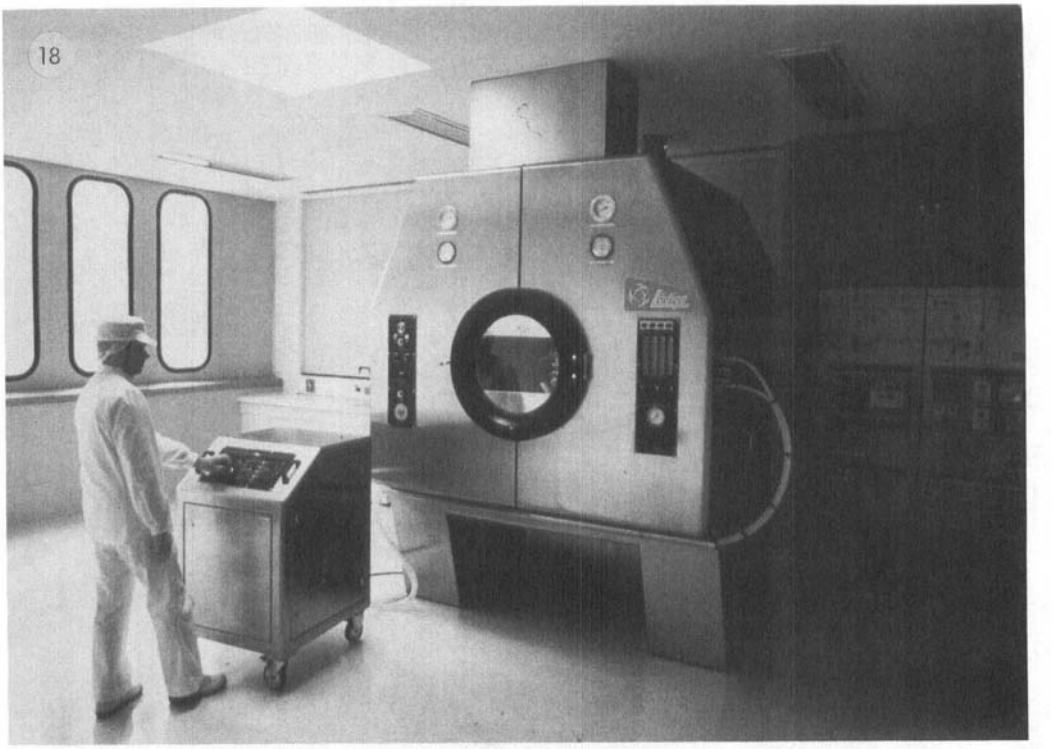

Figure 18.Automatic coating

Figure 19."self-control"

Figure 20.Balance of weighs for tablets (yield).

through a sieve, dried on air flow driers, calibrated, blended with lubricants. It can then be either tabletted and possibly coated or it can be put into hard gelatine capsules;

Photos will illustrate this scheme at the end of the lecture.

Principle

All steps of the manufacturing process to be computerized should first be defined. A table describing the whole process and precising the levels and the extent of computerisation can be helpful. This is the role of the table we have already seen.

Coherence of the whole system should be assessed: for example, it should be checked that it is impossible to process through step n + 1 if conditions required for step 1 have not been fullfilled.

The list of people who are authorized to enter data concerning one batch and the procedure to be used for the system to accept them. How and by whom it can be modified and if the procedure remains confidential and codes changed periodically.

Manufacturing formulas as printed should be checked against manufacturing procedures; the same for major points (.... time of blending for powders, temperatures for drying of wet mix...).

Alarms

Functions linked to alarms and their threshold should be determined for all critical steps.

Determine whether the thresholds could be altered by the operator. Determine what should be done when an alarm runs; this should of course be integral part of SOPs.

Are the alarms periodically checked and is it possible to assure that they are in state of running.

Determine whether the fact that alarms have run is indicated in the batch record or not.

Quality control

Sampling

The label printing system indicating sampling should also be able to work manually in case of failure.

Release of batches of finished or semi-finished products

It should be verified that :

- the input of a positive information really is independent from any direct responsability of manufacture services :
- the procedure for signature of QC is kept confidential and regularly modified.

Partinence of the system

Verify that not too many securities do exist, which would, in fact, lead to false securities.

CONCLUSION

Computers have become a need for the pharmaceutical industry, but, as any other machine, they should be controlled by users to quarantee quality assurance and pharmaceutical security.

Ensuring that pharmaceutical manufacturing systems work accurately, reliably and consistently, is a fundamental part of the responsibility of the industrial pharmacist.