In-Process Control

Paul Osborne September 2006

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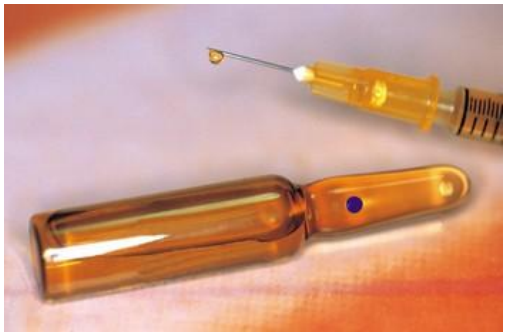
In-Process Control

- Chemical engineering - In-process methods are key components of quality control in a chemical manufacturing plant during an API manufacturing process . These methods ensure that a production reaction step will produce a quality chemical entity in the expected yields.
- Chemical processing differs from product manufacturing. For example, the manufacture of a finished product typically involves a molecular entity that is stable under normal conditions and can be stored for prolonged periods without losing its physical and chemical characteristics.



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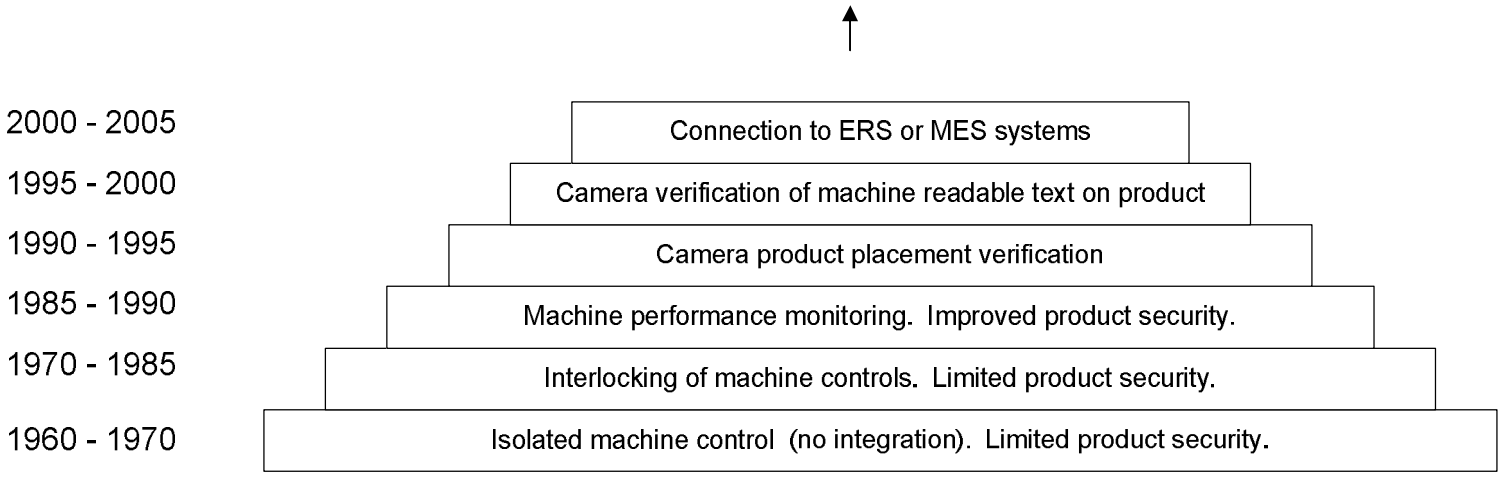
In-Process Control

- For packaging, in-process control has evolved over the last 30 years.
- As pharmaceutical packaging lines evolved, the interfaces between operating personnel and the equipment are also changing because of the merger in process between conventional electrical controls and information systems.
- This evolution can be described as follows:



ERP - Enterprise Resource Planning,
MES – Manufacturing Execution Systems

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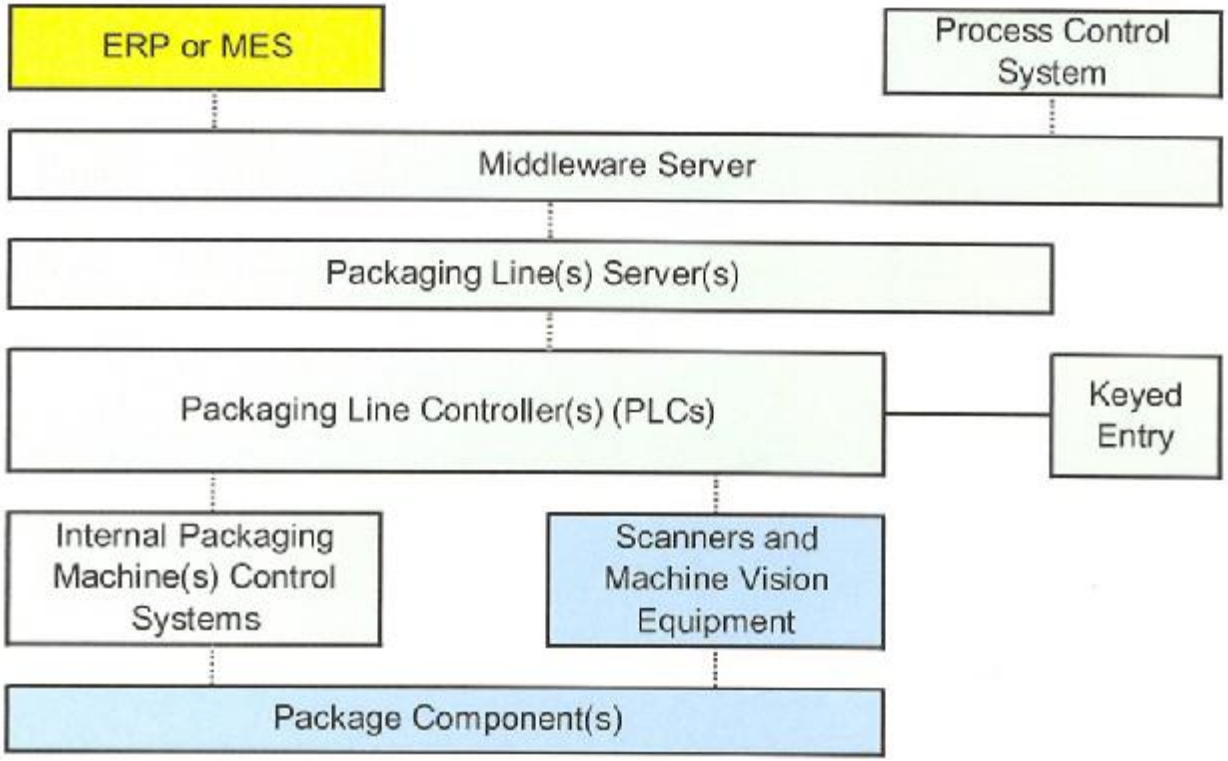
In-Process Control – Integration to the ERP or MES system



- The next evolution is at hand. With interfaces between the ERP or MES, the process control system, and the packaging line, the final connection has been made and complete logical automation of the data flow becomes reality.

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In-Process Control

- Perhaps the most dramatic evolution came with the start of bar code printing and scanning equipment, and later, with the increasing availability of optical vision systems.

- These systems not only verify that the actual bar code and the text that was printed matches the control data, but more importantly, that the printed information matches pre-print information, such as product label, insert, outsert, carton, and case or tray codes.

- While these systems have extensive capability and significantly advanced the state-of-the-art, they match from package component to package component and do not normally include the logical connection to the product source unless implemented by the owner.

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In-Process Control

- Control systems for packaging lines address a wide range of operational issues. All packaging lines have the need to ensure that the correct product is being delivered into the primary package – product security.
- Medium and high-speed packaging lines address the issue of product or equipment being damaged if a downstream machine stops or is running slower and the accumulation capacity is nearly full.
- Pharmaceutical packaging lines, among others, have the additional need to ensure that the codes being printed on the package are consistent with the product, the lot number, and the package.
- In the very near future, these same lines may also require the capability encode an RFID tag during packaging or associate an EPC with a specific case of product. These features also enhance the ability to assemble lot genealogy information – track and trace.

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In-Process Control – Bar codes

- Bar Code are used for optical readable (read only) identification.
- Example of Linear (1D) Bar Code Structure.
  - Use of linear (1D) Bar Code started 1968 with 2/5 interleaved symbol.

  - PHARMA-CODE has been used since 1969.

max. 131070

- Example of Stacked Bar Code Structure.

- Example of Matrix (2D) Bar Code Structure.

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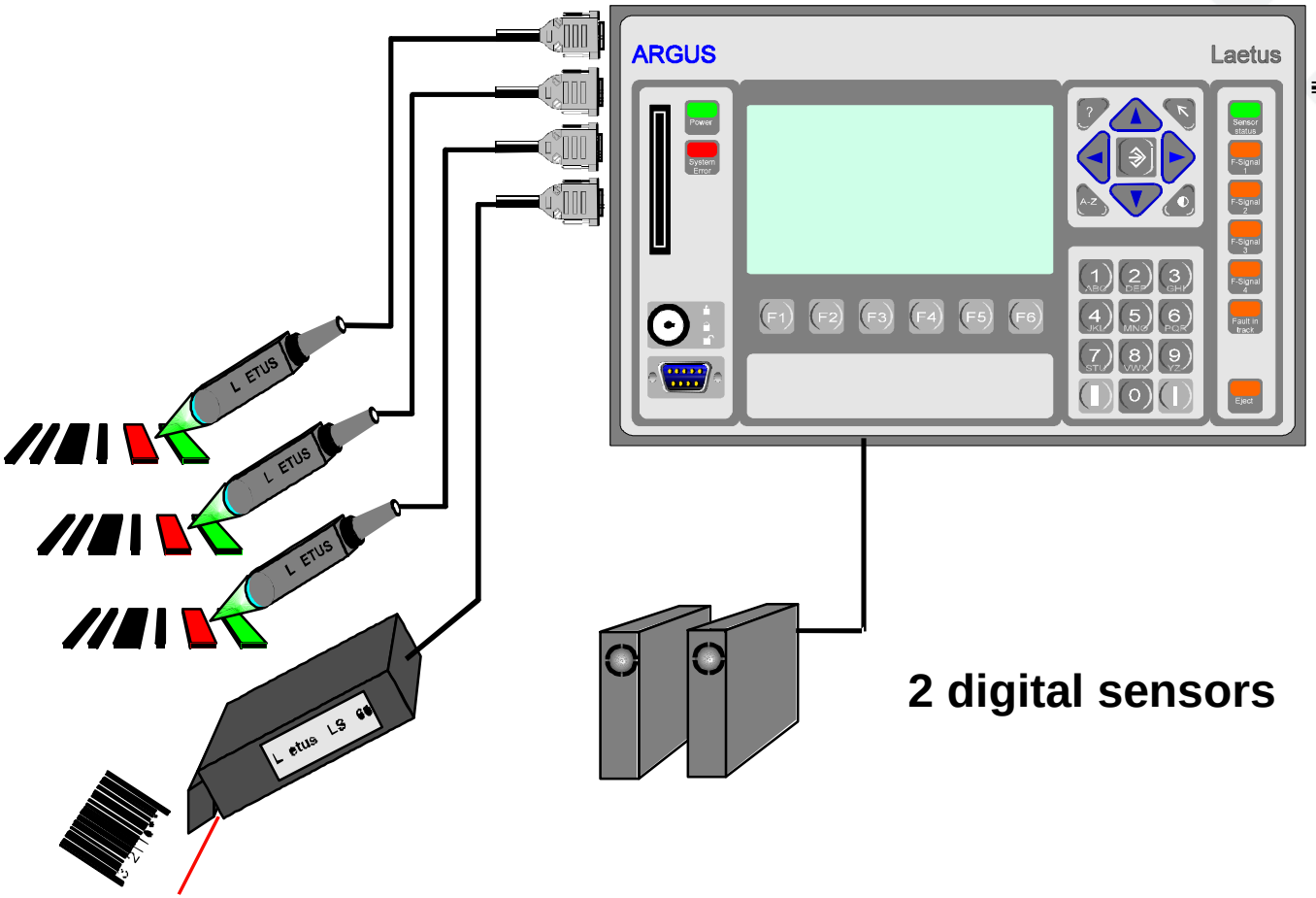
In-Process Control – Bar code reading



Output to machine PLC or eject

2 digital sensors

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In-Process Control – Machine Vision

- Smart Camera

Smart cameras include a sensor, a digital signal processor for analog-to-digital conversion, memory for temporary image storage and manipulation, and for operational software and algorithm storage.

- Matrix-CCD Resolution

Matrix camera resolution is classified by pixels. Sometimes definitions are used from the ‚PC World' (monitor).

- 640 x 480 pixel VGA (640 x 480)
- 800 x 600 pixel SVGA (800 x 600)
- 1000 x 800 pixel XGA (1024 x768)
- 1400 x 1000 pixel SXGA (1400 x 1050)

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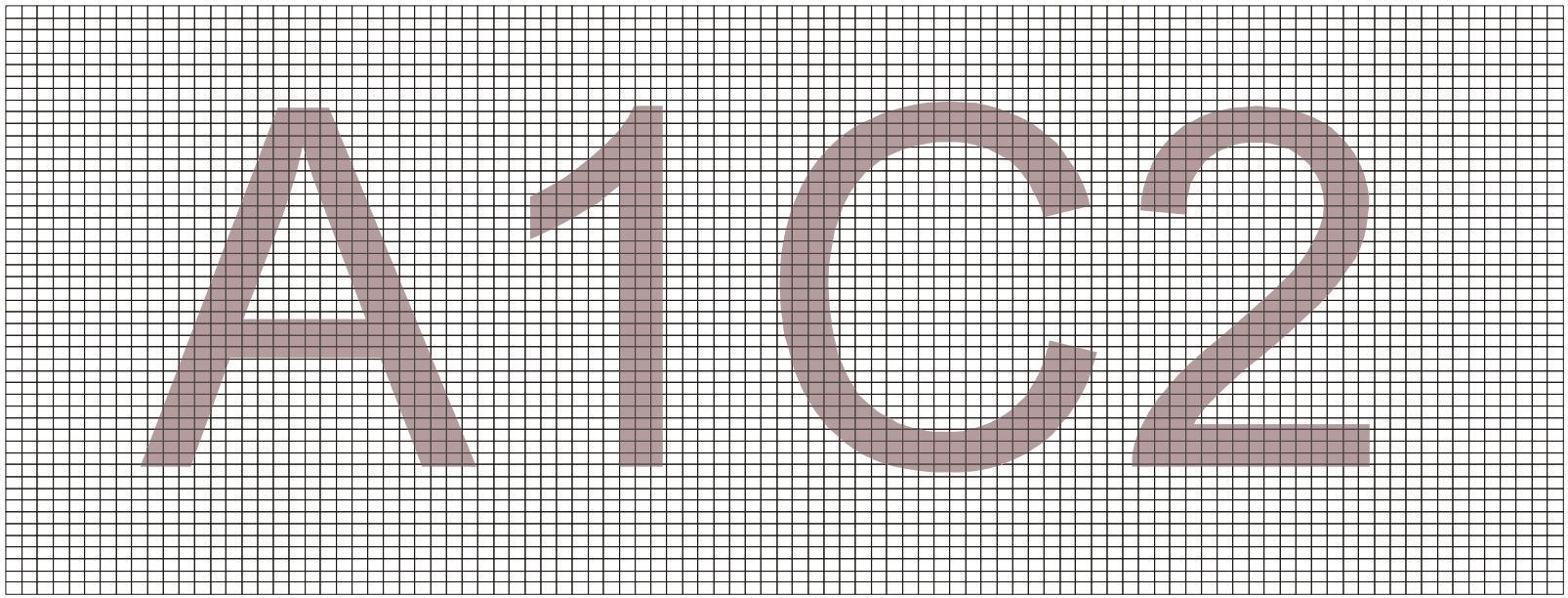
In-Process Control – Machine Vision

- Pixel - Picture element. The camera image is created from pixel oriented in rows and columns.

Sample with 150 x 50 pixel matrix.



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In-Process Control – Machine Vision

- Field of View - a rectangular, two dimensional, array of grey level values (pixels) created by a physical device, such as a camera.
- Area of Interest (AOI) or Region of Interest (ROI) a part of the field of view which contains objects of interest like text.
- Window - a part of the AOI containing located objects of interest.
- Mask - an area of a window containing an individual object of interest to be examined.

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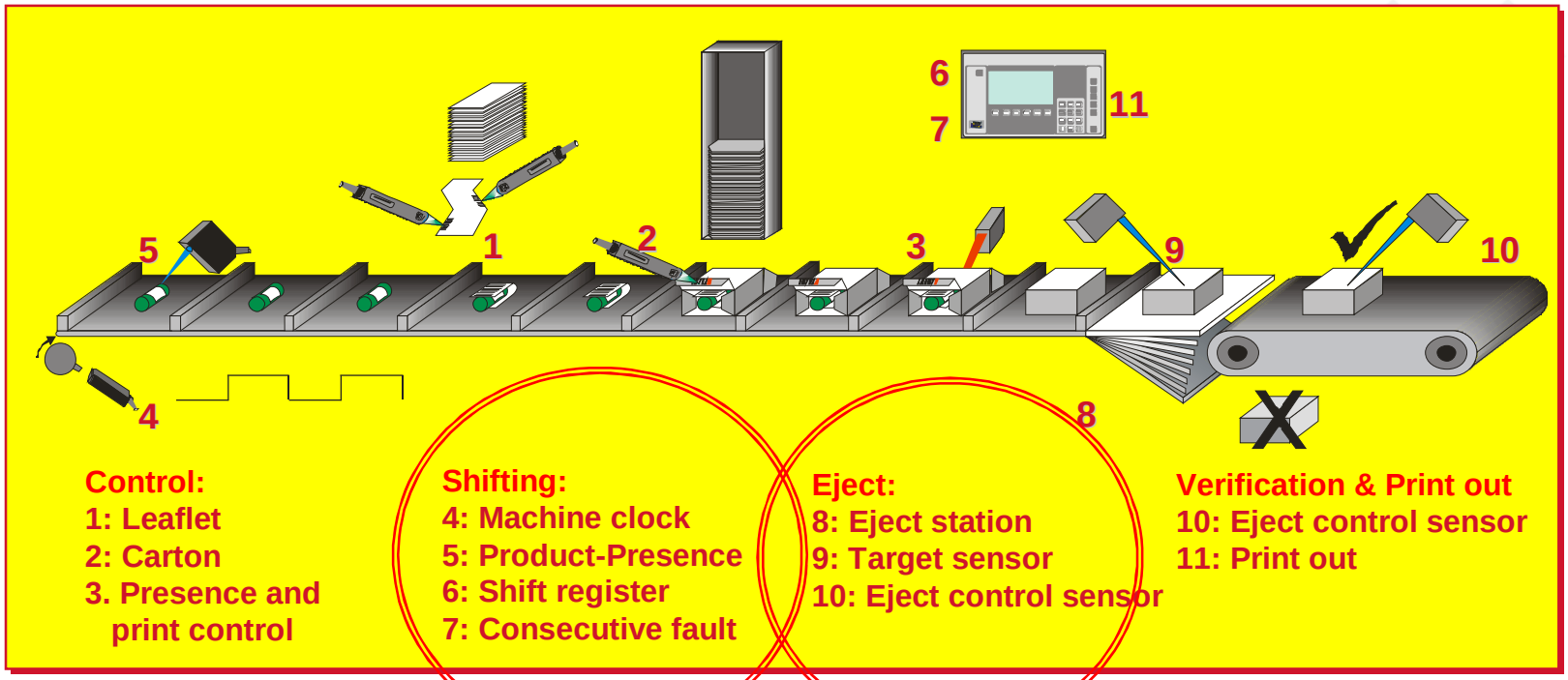
In-Process Control – Machine control



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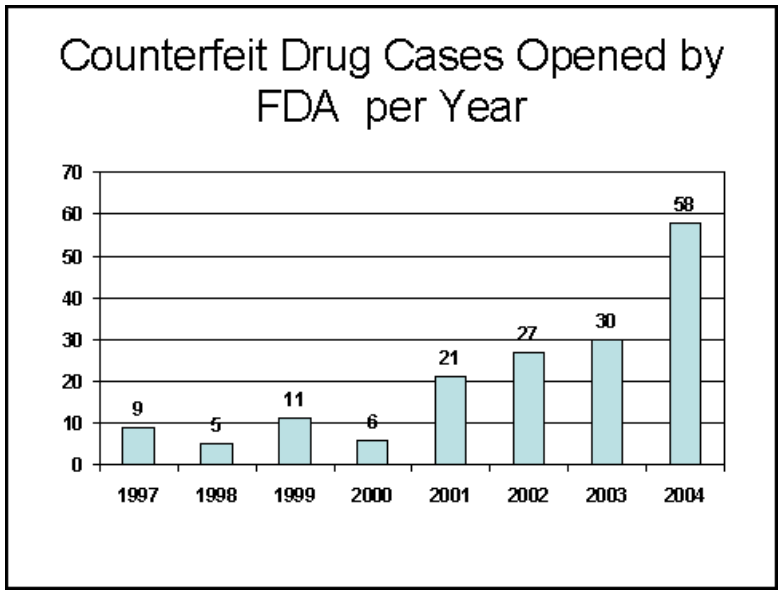
In-Process Control – Anti Counterfeiting, track and trace

- In the US and Europe a relatively comprehensive system of laws, regulations and enforcement by Federal and state authorities has kept drug counterfeiting rare. In recent years however, the FDA has seen growing evidence of efforts by increasingly well-organized counterfeiters in the USA.



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In-Process Control – Anti Counterfeiting, track and trace

- Track-and-trace is the ability to track each product, at the unit of use level, beginning with the moment it is manufactured, through distribution, and to the end customer.
- Authenticate and secure the product first at the unit of use. Then supply, track and trace only the authentic product
- To do this precisely, it is necessary to assign a unique serial number to each product at the individual package level. Thus identifying the product type and its origin.
- Databases collect and store these e-pedigrees, enabling the tracing of every product from its originating manufacturer and throughout the supply chain.
- Traditionally, 1D and 2D bar codes printed on product packages have served a purpose of tracking and tracing.
- Alpha Numeric is developed, along with Data Matrix codes and RFID.

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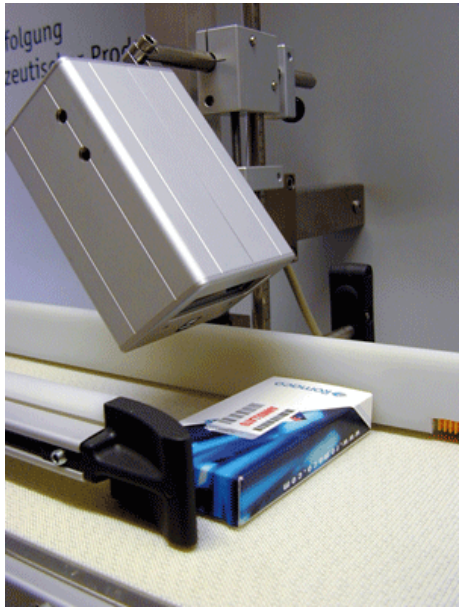
In-Process Control – Anti Counterfeiting, track and trace

- Serialized USA Lottery Game Security Printing (fifteen years ago)
- Serialized H.P. printer cartridges (ten years ago)
- Serialized Microsoft software (five years ago)
- The Italian Vignette declaration (five years ago)



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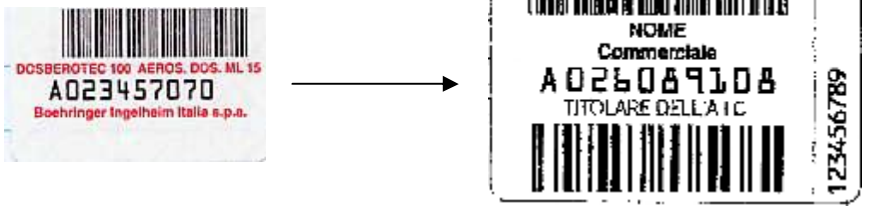
In-Process Control – Anti Counterfeiting, track and trace

- The Italian government have for many years provided individual pharmaceutical cartons with an external, peal-off vignette label containing a single bar code.
- As an anti-counterfeiting control and for improving the supply chain security to the end user, the Italian government has recently made law a modification to this vignette label. A new,unique, progressive 2/5i code was added.
- The Product code value plus the Progressive Interleaved 2/5 code value equals the Serial Number of the label.
- The plan is the complete elimination of losses due to theft and/or counterfeiting, this currently accounts for some 6% of the total pharmaceutical turnover.



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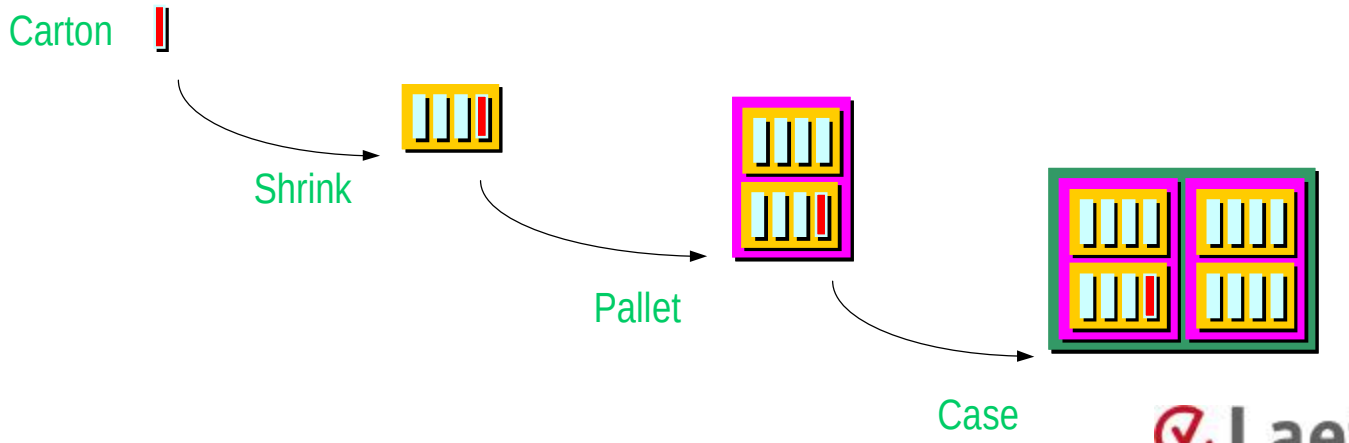
In-Process Control – Anti Counterfeiting, track and trace

- All data collected during the packing and tracking operation will be stored in a database, the construction of which allows the assignment of a unique identity to each product shipment, so that its contents can be identified at any time.
- For the time being the information in the database can be reproduced in list form; its design will however accommodate an online connection for upload of data to a central computer at the Italian Ministry of Health in the future.



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In-Process Control – Anti Counterfeiting, track and trace

- The FDA have stated that the use of RFID technology is critical to ensuring the long-term safety and integrity of the U.S. drug supply chain. A manufacturer will attach RFID tags to immediate containers, secondary packaging, shipping containers, and/or pallets of drugs. Pilot schemes were to be completed in 2007
- This expectation has not been achieved and certain individuals believe that this will be the case for years to come, why? Well here are some of the findings to date:

  - **Unlike bar codes and others, RFID can be have multiple readings within a pass of a batch of containers**
  - **RFID signals can be masked by a variety of pharmaceutical components, such as liquids**
  - **The cost of the individual tags remains high – *Tag economics***
  - **There is now concern over the radio frequency effects in close proximity to the API - *heating***
  - **Reliability issues, recent tests showed 0.5% failures – *bottle wrap stress***
  - **RFID tags can give away restricted information, lack of standards with respect to privacy.**
  - **Global data Standards - *waiting for global standards***

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In-Process Control – Unit dose identification

- On December 3, 2001 the FDA announced a proposed rule requiring that the National Drug Code (NDC) be bar-coded on all pharmaceutical and biological products,
- “Unit-dose packaging" means a method of packaging a product into a non-reusable container designed to hold a single dosage unit intended for administration directly from that container.
- The FDA announcement stated that it was also examining the requirement for lot number and expiry (expiration) date.
- It must be stated that the FDA do not specify which barcode symbology is to be used. The advantage of a well introduced linear symbols and the existing EAN•UCC system was mentioned.

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In-Process Control – Unit dose identification

- Within the area of very small healthcare items, the unit dose items dispensed to the patient at the hospital bedside has a high importance for correct product identification.
- The lack of possibilities for automatic identification leads to high manual effort and potential errors during medication, documentation or at the stock control stage. This was an area of concern for the FDA.

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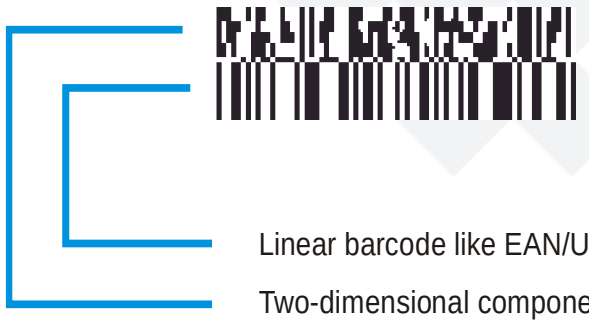
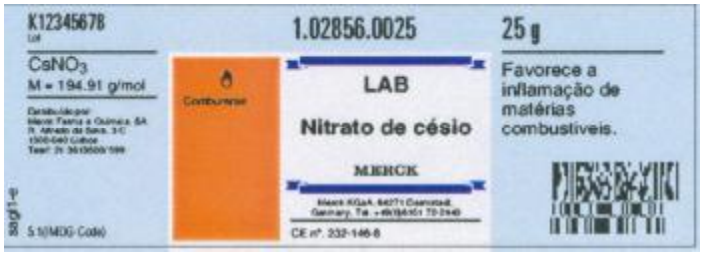
In-Process Control – Unit dose identification

- The UCC developed, patented and placed the Reduced Space Symbology and Composite 2D barcode component in the public domain in November 1999.
- The RSS code can be used as a linear symbol alone or with an additional composite symbol.
- The composite component can contain additional information related to the product. It is recommended to use the composite component to adopt the expiry date and the lot number, because this is legally required information.





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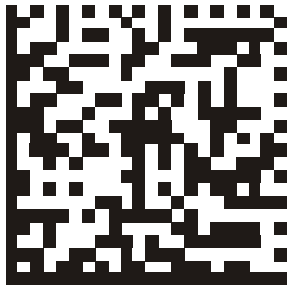
In-Process Control – Unit dose identification

- Additionally to the UCC solution the Health Industry Business Communications Council (HIBCC) made its own proposal.
- The HIBCC preferred solutions for small healthcare items is the Data Matrix Code.
- Some reasons stated by the HIBCC for the adoption of Data Matrix are because it is a better barcode than RSS. The following page shows the advantages of Data Matrix codes.



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In-Process Control – Unit dose identification

- Size - Data Matrix symbols as small as 2 mm can be accurately printed and read. RSS will not fit on all unit-of-use packages.

- Print Quality - Data Matrix can be decoded with as little as 20% contrast. RSS, like all linear barcodes, requires a higher level of print quality and contrast.
- Readability - Data Matrix can be marked directly on any surface including reflective materials such as foil packaging associated with some unit-dose blister packs.
- Error Correction - Data Matrix symbols employ Reed-Solomon error correction. RSS has no error-correction capability.
- Scaleable and omni-directional reading.

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Thank you
for your attention!

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