Visible particulate matter in parenterals is at the basis of many market recalls. Rubber closures are one of the potential sources of visible particulate matter in parenterals. Using rubber stoppers that are essentially free from detachable particulate matter therefore is an important factor that must be considered in the choice of drug packaging.

Pharmaceutical rubber stopper manufacturing consists of the following process steps:

1. Weighing of the raw materials according to a rubber formula recipe;
2. Mixing of the rubber ingredients in an internal mixer, followed by milling and intermediate storage;
3. Preforming of the mixed rubber by extrusion or calandering, followed by intermediate storage;
4. Moulding of the preforms into defined product shapes that are attached to a ‘waste sheet’, followed by intermediate storage;
5. Separation of the stoppers from the waste sheet by die-trimming, followed by intermediate storage;
6. Washing, siliconization and drying of the stoppers;
7. [Camera inspection = optional step that has restrictions as to the rubber product shape];
8. Packing of the stoppers into primary and secondary packaging;
9. Packing into tertiary packaging (cartons), palletization and shipping.

A scheme of these manufacturing steps is given below.

Of course the manufacturing of rubber stoppers for pharmaceutical applications takes place in production areas where the necessary cleanliness and tidiness measures are taken. However, with the exception of steps 6 thru 9, manufacturing generally does not take place in classified cleanrooms according to internationally recognized standards such as ISO 14644-1 or EU GMP Annex 1. It is clear that the above described manufacturing process, if not well managed, offers plenty of opportunities for visible particulate matter to enter and to potentially end up as detachable particles on finished rubber products or, in case of inadequate choices of packaging materials, to re-enter after packaging of the products. In subgroup 1 of the present A3P project on visible particulates, a collaborative exercise in the form of an FMEA analysis is taking place to systematically investigate into the sources of particulate matter and to rank their importance.

In the previous years efforts were undertaken to improve visible particulate cleanliness of rubber stoppers by a number of measures that had either a preventive character or a corrective character.
Without even attempting to give an exhaustive listing, preventative measures can be stated to be located in the areas that are described below:

• Clean building design
Pharmaceutical stopper manufacturing not seldomly was taking place in manufacturing areas that were constructed 30 or more years ago, when the criticality of stopper cleanliness was recognized, but was not so much at the forefront as it is today. Moreover, these buildings had grown over time, whereby e.g. compromises had to be made with respect to the logical flow of materials, resulting in repeated exposure of products in the various stages of the manufacturing process to non-optimized environmental conditions. In more recently constructed buildings, a strict zoning concept using clean building rules and clean materials of construction, allowing for more space between individual manufacturing equipment and with optimized material flows and reduced intermediate storage, was adopted from the start on. Also other aspects as e.g. creating better lighting conditions were part of the building design.

• Personnel gowning
As is the case in aseptic drug manufacturing with respect to biological and particulate contamination, operating personnel in stopper manufacturing areas is an important potential source of particulate matter. Other than in aseptic manufacturing, automation in a rubber plant, in view of the complex manufacturing process, is at a considerably lower level. Manufacturing rubber parts to a certain extent can be automated, but operating personnel that carries out activities of higher physical intensity, remains necessary. Efforts have been made to increase the level of automation, allowing to reduce the number of operating personnel. This is particularly relevant for the final stages of the process, at and after washing, since products then are in their best state of cleanliness. Additional measures have been taken to progressively limit the exposure of operators to products by improving their gowning itself and by imposing stricter gowning rules. The latter ranges from the constant covering of hands and forearms in all stages of the process to wearing full clean room garments in the area where washed products are being handled for additional camera inspection and for packing. An additional measure to control exposure of man to the product was to restrict the access to manufacturing areas, including visitors.

• Training
To increase the awareness of operating personnel more resources are being spent on their training and retraining. These efforts are not limited to the ‘genuine’ manufacturing personnel, but also include cleaning and maintenance personnel who enter production facilities less frequently. For external auditing personnel who need to enter the manufacturing areas, the same gowning rules apply as for operating personnel.

• Shielding of products from the environment
No matter how good the building and the construction materials are, the environment remains a potential source of particulate contamination. Therefore it is always beneficial to maximally shield the products from the environment in the various stages of the process. In stopper manufacturing this has been improved e.g. by introducing the use of closed containers in all stages of intermediate storage and to limit their exposure to the environment to the restricted time that is needed for the active parts of the mixing, moulding and die-trimming cycles.

• Lean manufacturing / faster throughput
Restriction of product exposure was also facilitated by adopting certain principles of lean manufacturing, that lead to faster throughput of items.

• Improved cleaning
Improved cleaning procedures were adopted for both the manufacturing environment and for the manufacturing equipment, including all equipment used for intermediate storage between mixing and moulding, between moulding and die-trimming, between die-trimming and washing and so on. The improvements pertain to both the robustness of the cleaning operations and the frequency with which they are applied.

• Monitoring of the production environment
Monitoring of the state of cleanliness of production areas and of utilities, particularly towards the end of the total process, has made its way into rubber stopper manufacturing for already a longer time. In more newly constructed plants however, the scope of monitoring could be expanded from the start on. The possibility was there to bring monitoring data and equipment and utility alarms together in overarching systems.

• Improving cleanliness of primary packaging material
Longer term work is almost continuously being devoted to improving cleanliness of primary packaging material. These efforts relate to the manufacturing processes and manufacturing environment of converters that supply primary packaging materials, as well as to the controls of their operations and finished products with respect to particulate cleanliness.

Prevention of the creation of visible particulate matter is a necessary action, however it is illusory that no particles end up on the products.
As a corrective measure the closure manufacturer still disposes of two process steps to remediate:

• The final washing process
The final washing of rubber products has multiple purposes. One of them is to bring the products in a controlled state of microbiological cleanliness, another one is to bring them in their final state of particulate cleanliness. Therefore one of the objectives of stopper washing is to remove detachable particulate matter that is present after die-trimming. For doing so, washing process parameters such as the number and duration of detergent steps, temperature at washing, detergent concentration, the number of rinsing steps, the volume of rinsing water spent per product, etc. need to be optimized. The same holds for the parameters of the drying cycle, such as temperature at drying and the duration of the cycle. It is a fact that particulate cleanliness of rubber products can be deteriorated by excessive drying.
Camera inspection after washing and drying
The primary purpose of camera inspection is not to reject products with detachable particulate matter, but rather to reject products with embedded particles that are perceived as ‘cosmetic’ defects. Notwithstanding this, camera inspection will also detect loose particulate matter on stoppers such as firmly attached rubber particles that have persisted during washing and rinsing. It is needless to say that camera detection technology, both in terms of camera hardware and of computer software is constantly evolving. Staying up-to-date on these technological evolutions is certainly to the benefit of the closure manufacturer, of its customers and ultimately… of the patient.

Conclusion
Improvement of visible particulate cleanliness of elastomeric closures for parenteral use can be promoted by application of a series of operational measures that fall apart in two classes. On one hand preventive measures limit the presence of such particles, on the other hand corrective measures at the end of the manufacturing process, to the limits of technical feasibility, eliminate defective parts that still have formed.