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(54) Title: SYRINGE BARREL LUBRICANT COVERAGE QUALITY CONTROL

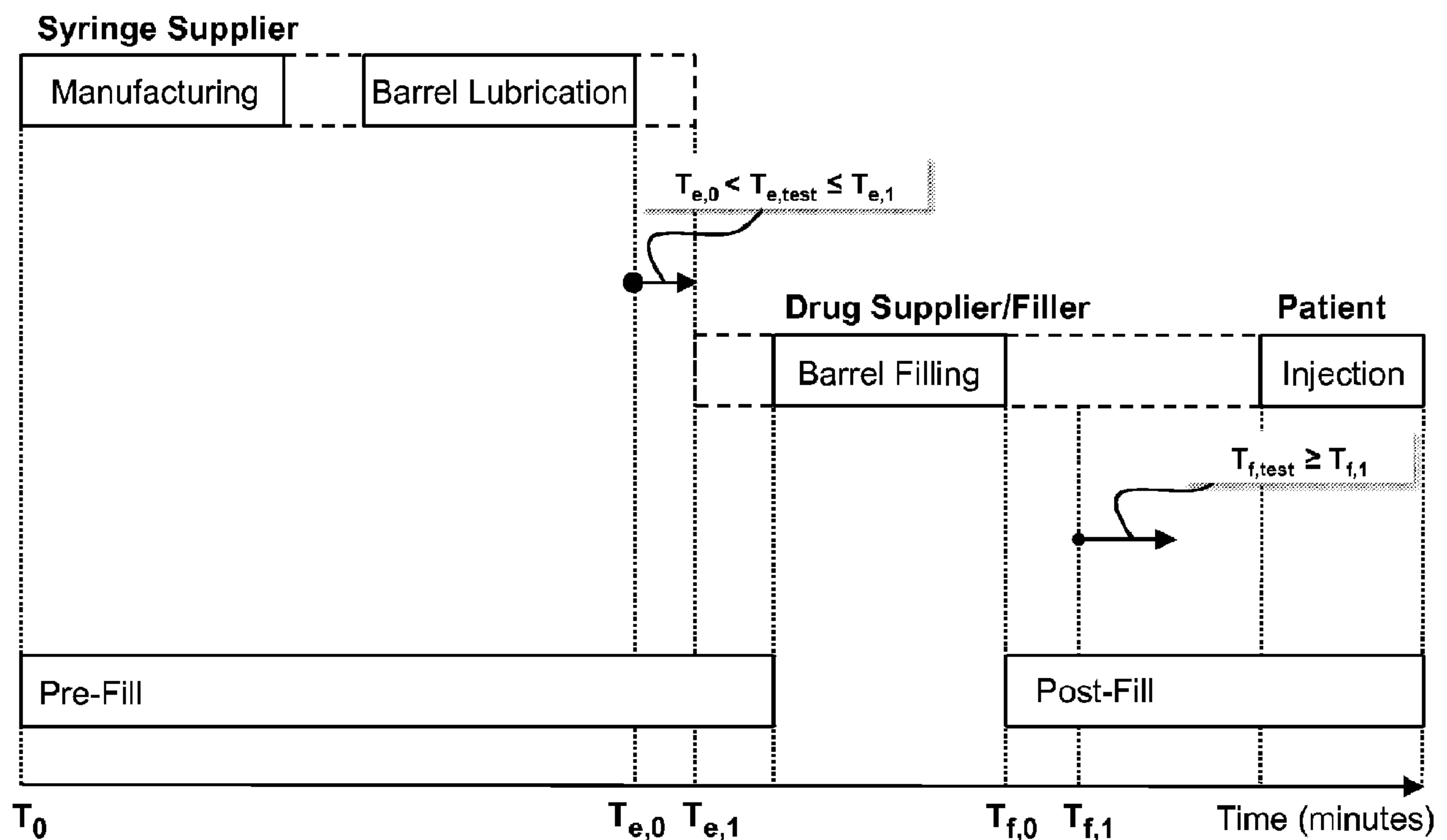


FIG. 1

[] = delay/shipping/storage

100

(57) Abrégé/Abstract:

A quality control method or system for determining a lubricant coverage at the inside surface of a syringe barrel is provided. The timing for the quality control is not intuitive, yet crucial for patient's safety. The pre-fill test is for a pre-filled (empty or no drug



(57) **Abrégé(suite)/Abstract(continued):**

solution), yet oil lubricated, barrel. This pre-fill test needs to be performed within a certain time window immediately following the lubrication. The post-fill test is for a post-filled oil lubricated syringe barrel filled with a solution. This post-fill test needs to be performed after a certain time window has passed from the filling with the solution. The quality control methods could lead to a reduction of health-risks or avoid life- threatening situations associated with syringes that are either below or above the desired lubrication coverage.

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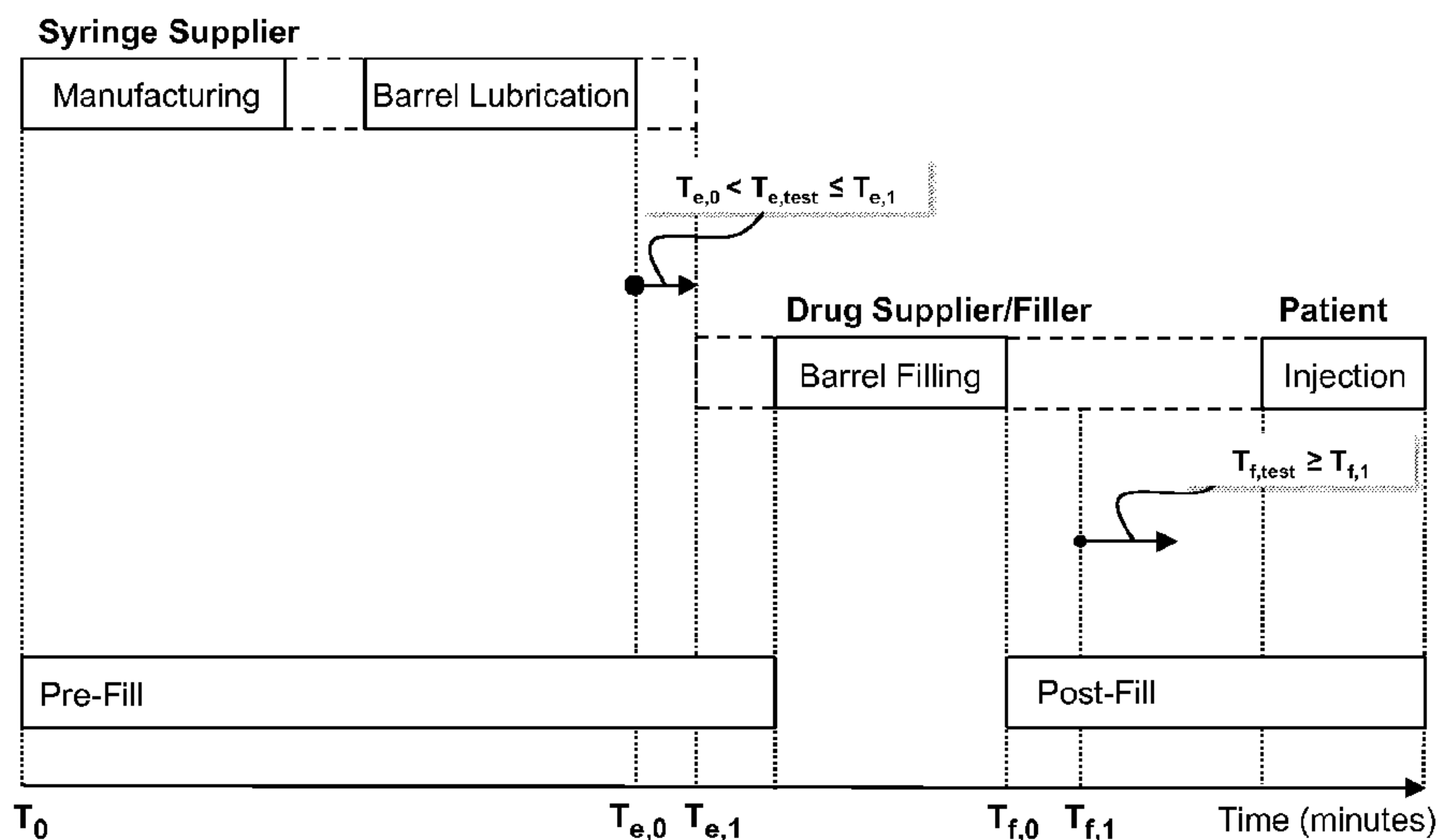


FIG. 1

[] = delay/shipping/storage

(57) **Abstract:** A quality control method or system for determining a lubricant coverage at the inside surface of a syringe barrel is provided. The timing for the quality control is not intuitive, yet crucial for patient's safety. The pre-fill test is for a pre-filled (empty or no drug solution), yet oil lubricated, barrel. This pre-fill test needs to be performed within a certain time window immediately following the lubrication. The post-fill test is for a post-filled oil lubricated syringe barrel filled with a solution. This post-fill test needs to be performed after a certain time window has passed from the filling with the solution. The quality control methods could lead to a reduction of health-risks or avoid life-threatening situations associated with syringes that are either below or above the desired lubrication coverage.

SYRINGE BARREL LUBRICANT COVERAGE QUALITY CONTROL

FIELD OF THE INVENTION

5 The invention relates to quality control methods and system for syringe barrels. In particular, the invention relates to quality control of lubricant coverage at the inner surface of a syringe barrel.

BACKGROUND OF THE INVENTION

10 Syringes already filled with an aqueous-based drug solution play an increasingly important role in the pharmaceutical industry and the medical community. For the purposes of this invention, such filled syringes are defined to as post-filled syringes; i.e., post/after the time of filling the syringe with the solution, which is in contrast to pre-filled, which is defined for the
15 purposes of this invention to as prior/before the time of filling the syringe with the solution.

Within the industry community, post-filled syringes represent a market share of over \$2 billion dollars, with over 60 products on the market and a growing
20 number of protein-based products expected to enter the market in the near future.

From a medical standpoint, post-filled syringes allow for improved drug

delivery that is less wasteful, safer, and frequently easy enough for patients to do without the oversight of a medical professional.

An important part of the syringe is the plunger system, which relies on a layer
5 of lubricant to allow for ideal glide force and ensuring complete delivery of the drug product.

The most common lubricant is silicone-based oil, and the siliconization of these syringes, understandably has played an important part in the
10 development of pre-filled syringes. As well as providing an ideal glide force and ensuring that the plunger travels the full path, siliconization also provides several advantages. It is a hydrophobic oil allowing for easy emptying of a drug product, and the oil is low reacting, frequently used as a buffer layer between the syringe barrel and the drug product ensuring no reaction takes
15 place between the two materials.

This has led to the use of siliconization in other applications beyond the post-filled syringe market, such as use as coating in vials and ampules in some cases. Siliconization is a widely used process that has been often overlooked
20 and under-championed, despite its use, and manufacturing concerns over proper siliconization and the demands for testing to determine uniform coverage have often gone overlooked. An example of this is the Amgen recall of 2006 in Europe, requiring millions of drug product to be returned as improper siliconization was to blame for improper dosing.

As important as this process is, several manufacturing concerns are still being dealt with to-date. Too *much* silicone oil can lead to protein aggregation and too *little* oil can be telling of an improper spraying within the manufacturing environment. Protein aggregation has the potential to produce improper antibodies within the drug that on delivery could cause an unwanted, potentially fatal response in a human. In systems with agitation, the protein build-up is significant enough to be observed visually with the naked eye. Also, large amounts of sprayed oil have led to oil droplets within the drug product.

For sensitive applications, such as injections into the human eye for treatment, silicone oil droplets are observable within patients with an unknown amount of damage. As the FDA and other governing bodies work to not only establish the danger of these and other leachables, it is important to develop technology that will allow the greatest amount of quality control over the manufacturing process. The only way to guarantee high-quality coatings being delivered is through 100%, high-speed inspection of pre-filled and/or post-filled syringes, which is the topic of this invention.

SUMMARY OF THE INVENTION

A quality control method or system is provided for determining a lubricant coverage at the inside surface of a syringe barrel for a *pre*-filled and *post*-filled

syringe barrel. For the purposes of this invention, post-filled syringes are defined as syringes post/after the time of filling the syringe with the solution, which is in contrast to pre-filled syringes, which are defined for the purposes of this invention to as prior/before the time of filling the syringe with the
 5 solution.

For the *pre*-filled syringe barrel, an un-filled/pre-filled syringe barrel is provided having an inner surface, where the inner surface has not yet been covered with a lubricant. A lubricant is applied to cover to the inner surface
 10 of the pre-filled syringe barrel using a lubricant covering device, therewith creating a lubricant-covered pre-filled syringe barrel. Prior to filling the lubricant-covered barrel with an aqueous-based solution, one or more pre-fill optical properties are obtained of the lubricant-covered pre-filled syringe barrel. The pre-fill optical properties are obtained at a time T_e defined as

$$15 \quad T_{e,0} < T_e \leq T_{e,1}$$

where $T_{e,0}$ is the time of the applying the lubricant, where

$$T_{e,1} = 0.05\eta$$

defined in minutes, where η is a viscosity of the applied lubricant and defined in cSt, and where the pre-fill optical properties are obtain using a first imaging
 20 system. A pre-fill quality measure is determined for the lubricant-covered pre-filled syringe barrel using the pre-fill optical properties as input to a computer-implemented pre-fill barrel quality measure determination program executed on a first computer. The pre-fill quality measure is used by a first

syringe processing system to reject or accept the lubricant-covered barrel based on a predetermined pre-fill quality threshold.

For the *post*-filled syringe barrel, a lubricant-covered un-filled/pre-filled syringe barrel is provided, where the lubricant-covered pre-filled syringe barrel has not yet been filled with an aqueous-based solution. The lubricant-covered pre-filled syringe barrel is filled with an aqueous-based solution (e.g., an aqueous-based drug-containing solution) using an aqueous-based solution filling device, therewith creating a lubricant-covered post-filled syringe barrel.

One or more post-fill optical properties are obtained of the filled lubricant-covered syringe barrel, where the one or more post-fill optical properties are obtained at a time T_f defined as

$$T_f \geq T_{f,1},$$

where

$$T_{f,1} = 8.8 \exp(0.0063\eta)$$

defined in minutes and defined from $T_{f,0}$, where η is the viscosity of the applied lubricant and defined in cSt, where $T_{f,0}$ is the time of the filling the aqueous-based solution, and where the post-fill optical properties are obtained using the first imaging system or a second imaging system. A post-fill quality measure is determined for the filled lubricant-covered barrel using the post-fill optical properties as input to a computer-implemented post-fill barrel quality measure determination program executed on the first computer or a second computer. The post-fill quality measure is used by the first syringe processing

system or a second syringe processing system to reject or accept the filled lubricant-covered barrel based on a predetermined post-fill quality threshold.

To guarantee or significantly improve high-quality coatings for syringe barrels
5 needs to occur through 100%, high-speed inspection of pre-filled as well as post-filled syringes along the processes specified in this invention. Failure to perform both these quality tests, i.e. at both stages of the processing pipeline, may lead to serious consequences and health issues, which could manifest when poorly or inadequately tested syringes are used on patients.

10

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the timing and process **100** of syringe barrel testing in the pre-fill and post-fill stages of the process according to an exemplary embodiment of the invention.

15 **FIG. 2** shows a flow diagram **200** involving the systems/devices involved in pre-fill barrel lubricant coverage testing according to an exemplary embodiment of the invention. The arrow indicates direction of the flow diagram.

FIG. 3 shows a flow diagram **300** involving the systems/devices
20 involved in post-fill barrel lubricant coverage testing according to an exemplary embodiment of the invention. The arrow indicates direction of the flow diagram.

FIG. 4 shows a flow diagram **400** involving the systems/devices involved in pre-fill and post-fill barrel lubricant coverage testing according to an exemplary embodiment of the invention. The arrow indicates direction of the flow diagram.

5 **FIG. 5** shows a timeline **500** of images for a plastic syringe barrel obtained by the imaging systems at different time steps of the pre-fill and post-fill barrel lubricant coverage testing process according to an exemplary embodiment of the invention.

10 **FIG. 6** shows a timeline **600** of images for a glass syringe barrel obtained by the imaging systems at different time steps of the pre-fill and post-fill barrel lubricant coverage testing process according to an exemplary embodiment of the invention.

15 **FIG. 7** shows according to an exemplary embodiment of the invention images **700** of an empty/pre-fill plastic syringe barrel (without lubricant).

FIG. 8 shows according to an exemplary embodiment of the invention images **800** of a pre-fill plastic barrel containing lubricant on the interior surface of the barrel immediately after spraying with oil.

20 **FIG. 9** shows according to an exemplary embodiment of the invention images **900** of a post-fill barrel containing lubricant on the interior surface of the barrel 3 minutes after filling with an aqueous-based solution.

FIG. 10 shows according to an exemplary embodiment of the invention images **1000** of a post-fill barrel containing lubricant on the

interior surface of the barrel 9 minutes after filling with an aqueous-based solution.

FIG. 11 shows according to an exemplary embodiment of the invention images **1100** of a post-fill barrel containing lubricant on the interior surface of the barrel 10 minutes after filling with an aqueous-based solution.

FIG. 12 shows according to an exemplary embodiment of the invention images **1200** of an empty/pre-fill glass syringe barrel (without lubricant).

FIG. 13 shows according to an exemplary embodiment of the invention images **1300** of a pre-fill glass barrel containing lubricant on the interior surface of the barrel immediately after spraying with oil.

FIG. 14 shows according to an exemplary embodiment of the invention images **1400** of a post-fill barrel containing lubricant on the interior surface of the barrel 7 minutes after filling with an aqueous-based solution.

FIG. 15 shows according to an exemplary embodiment of the invention images **1500** of a post-fill barrel containing lubricant on the interior surface of the barrel 22 minutes after filling with an aqueous-based solution.

FIG. 16 shows according to an exemplary embodiment of the invention images **1600** of a post-fill barrel containing lubricant on the interior surface of the barrel 3 days after filling with an aqueous-based solution.

FIG. 17 shows according to an exemplary embodiment according to the invention the time decay of detected optical features in an empty (pre-fill) plastic and glass syringe barrel after spraying the interior surface of the barrel with oil of viscosity 20 cSt.

5 **FIG. 18** shows a syringe according to an exemplary embodiment according to the invention.

FIG. 19 shows an imaging system setup according to an exemplary embodiment according to the invention.

10 **DETAILED DESCRIPTION**

Definitions

- *Post*-filled syringes are defined as syringes post/after the time of filling the syringe with the solution.
- *Pre*-filled syringes are defined to as prior/before the time of filling the
15 syringe with the solution.

The lubrication of a syringe barrel with oil and its distribution plays a vital role in the performance of the syringe since it allows for a reliable and consistent motion of the plunger in the syringe barrel. Since the lubricating oil
20 is transparent, and is applied to a transparent barrel (e.g., plastic or glass), a simple visual inspection of the syringe *cannot* ensure that there is adequate or any coverage of the lubricant in the syringe.

Embodiments of the invention can be used in two separate, yet complimentary scenarios within the pharmaceutical industry (**FIG. 1**). The first scenario involves the syringe manufacturer/supplier who can use the method
5 immediately following the spraying of the lubricant, while the syringe is still in a pre-fill stage, to inspect the interior surface of the barrel and to verify that it is coated with adequate coverage to ensure good device performance. The timing for inspection ($T_{e,test}$) for adequate (pre-fill) coverage is not intuitive, yet crucial for the quality control and further handling of the syringe.

10

The second scenario involves the drug-supplier/filler side of the industry. While drug manufacturers order syringes and insist that they have been inspected for lubricating oil coverage, the dynamic nature of a thin-film liquid lubricant coating can allow for migration, especially in an uncontrolled
15 shipping environment where temperatures can vary. Due to these issues it is of utmost importance for drug manufacturers/fillers to inspect the distribution of the lubricating oil. Incoming samples should be inspected immediately after being received to guarantee good performance of the product. Since empty (pre-filled) syringes may be stored with the drug manufacturer in
20 excess of months, it is important that the syringe be inspected again after being filled with an aqueous-based solution so as to provide a safe, reliable product to the consumer. The timing for this inspection ($T_{f,test}$) for adequate (post-fill) coverage upon filling the syringe with an aqueous-based solution is not intuitive, yet crucial for the quality control and further handling of the

syringe.

Implementing the inspection processes embodied in this invention at both the suppliers and the drug manufacturer's facilities will guarantee that a high-quality, reliable product will be provided to the consumer, without or at least a significant reduction of oil lubrication problems.

BARREL LUBRICATION

Upon the manufacturing of a syringe barrel, a lubricant is applied ($T_{e,0}$) to the inner surface of the barrel using a lubricant covering system (**FIGs. 1-6**). An imaging system is then used immediately after the barrel lubrication to obtain one or more pre-fill optical properties, i.e., prior to the filling of the barrel with an aqueous-based solution. As mentioned *infra*, the timing of testing ($T_{e,test}$) for adequate coverage is not intuitive and needs to occur *on or before* $T_{e,1}$ (**FIGs. 1, 5-6**).

When the barrel is sprayed with oil, the oil arrives on the inside barrel surface as droplets. The droplets are visible because of refractive index changes caused by the presence of droplets. The droplets merge into a uniform oil layer with time and the uniform oil layer does not show any detectable features related to the oil lubrication. Only the defects in the barrel are visible when the oil layer is uniform. A comparison of images **530/540** or **630/640** (image after $T_{e,test}$) with respectively images **510** or **610** (empty pre-lubricated barrel) in respectively **FIG. 5** or **FIG. 6** illustrates these effects and stresses

the importance as it becomes clear that delayed testing beyond $T_{e,test}$ will result in incorrectly concluding that the barrel has no or insufficient oil coverage where in fact it was adequately covered as evidenced by images **520** or **620** in respectively **FIG. 5** or **FIG. 6**. A barrel without performing a timely

5 $T_{e,test}$ could have been rejected or another application of a lubricant could have been applied resulting in too much lubricant coverage as discussed *infra*.

In general, the time $T_{e,test}$ is defined as

10
$$T_{e,0} < T_{e,test} \leq T_{e,1},$$

where $T_{e,0}$ is the time of applying the lubricant, where

$$T_{e,1} = 0.05\eta$$

15 defined in minutes, and where η is a viscosity of the applied lubricant defined in cSt. The pre-fill optical properties are, for example, optical changes related to the applied lubricant, changes in refractive index, or optical features of the lubricant.

20 The optimum time for inspection of empty (pre-fill) yet lubricated barrels depends on the viscosity of the lubricant. According to the formula the optimum time for inspection of an empty barrel for a lubricant with a viscosity

of 20 cSt is less than 1 minute and for a lubricant with a viscosity of 1000 cSt is less than 50 minutes.

A pre-fill quality measure (e.g., average number of features detected per cm², see also *infra*) is determined for the lubricant-covered barrel using one or more of the pre-fill optical properties as input to a computer-implemented pre-fill barrel quality measure determination program executed on a computer. A syringe processing system to reject or accept the lubricant-covered barrel based on a predetermined pre-fill quality threshold uses the pre-fill quality measure as input.

BARREL FILLING

Upon barrel lubrication, the barrel is filled ($T_{f,0}$) with an aqueous-based solution (e.g., a drug solubilized in water) using a solution filling device (FIGs. 1-6). An imaging system is then used after the barrel filling to obtain one or more post-fill optical properties, i.e., post to the filling of the barrel with an aqueous-based solution. As mentioned *infra* the timing of testing ($T_{f,test}$) for adequate coverage is not intuitive and needs to occur *on or after* $T_{f,1}$ (FIGs. 1, 5-6). In other words, in contrast to the pre-fill testing, the post-fill test is not immediately after the barrel filling, but significantly delayed.

In the post-fill testing case the uniform layer of oil starts to bead up over time because oil and water are immiscible. When the beads start to form the image becomes visible because of the changes in the optical features (e.g., refractive

index) (**550** or **650** in respectively **FIG. 5** or **FIG. 6**). It is noted that this post-fill evaluation process is the reverse of the physical/chemical process (beads to uniform oil layer) described *infra* for the pre-fill evaluation process of empty barrels with oil. In other words, the post-fill test has to be done *on or after* a
 5 certain amount of time ($T_{f,test}$) to see the beads of oil at the inner surface of the barrel. A post-fill barrel without performing the test *on or after* $T_{f,test}$ could have been rejected or another application of a lubricant could have been applied resulting in too much lubricant coverage as discussed *infra*.

10 For the case of the filled glass barrel with 1000 cSt viscosity oil, inspecting the barrel for the presence of oil in a shorter time than 3 days would lead to the conclusion that there is no oil in the barrel because the oil droplets would not yet have formed and the image would show little to no detectable features.

15 In general, the time $T_{f,test}$ is defined as

$$T_{f,test} \geq T_{f,1},$$

where

20

$$T_{f,1} = 8.8 \exp(0.0063\eta)$$

defined in minutes and defined from $T_{f,0}$, where η is the viscosity of the applied lubricant and defined in cSt, and where $T_{f,0}$ is the time of the filling the aqueous-based solution. The post-fill optical properties are, for example optical changes related to the applied lubricant, changes in refractive index or
5 optical features of the lubricant.

A post-fill quality measure (e.g., average number of features detected per cm^2 , see also *infra*) is determined for the lubricant-covered barrel using one or more of the post-fill optical properties as input to a computer-implemented
10 post-fill barrel quality measure determination program executed on a computer. A syringe processing system to reject or accept the filled lubricant-covered barrel based on a predetermined post-fill quality threshold uses the post-fill quality measure as input.

15 IMPLEMENTATIONS

FIG. 2 shows an example where the pre-fill testing is performed at the syringe supplier company using its own lubricant filling system, imaging system, computer, and syringe processing system respectively referred to as first. **FIG. 3** shows an example where the post-fill testing is performed at the
20 syringe filling or drug supplier company using its own solution filling device, imaging system, computer, and syringe processing system respectively referred to as second. **FIG. 4** shows an example where the pre-fill and post-fill testing are performed at the same company or facility using a its own

lubricant covering system, solution filling device, imaging system, a computer, and a syringe processing system respectively and where applicable referred to as first. A person skilled in the art would appreciate that different scenarios and combination of devices/systems can be used to fulfill the testing
5 requirements of this invention.

EXEMPLARY RESULTS

FIG. 5 shows a timeline **500** of images for a plastic syringe barrel (West Pharma 1 mL Long Syringe, 51.6 x 8.15 mm) obtained by the imaging
10 systems at different time steps of the pre-fill and post-fill barrel lubricant coverage testing process according to an exemplary embodiment of the invention. Image **510** is of an empty/pre-fill syringe barrel at time T_0 , image **520** is of a pre-fill barrel containing lubricant on the interior surface of the barrel immediately after spraying with oil at time $T_{e,0}$, image **530** is of a post-
15 fill barrel containing lubricant on the interior surface of the barrel 3 minutes after filling ($T_{f,0}$) with an aqueous-based solution at time $T_{f,0} + 3$ minutes, image **540** is of a post-fill barrel containing lubricant on the interior surface of the barrel 9 minutes after filling ($T_{f,0}$) with an aqueous-based solution at time $T_{f,0} + 9$ minutes, and image **550** is of a post-fill barrel containing lubricant on
20 the interior surface of the barrel 10 minutes after filling ($T_{f,0}$) with an aqueous-based solution at time $T_{f,0} + 10$ minutes.

FIG. 6 shows a timeline **600** of images for a glass syringe barrel (Schott glass, 2.25 mL, 54.4 x 10.85 mm) obtained by the imaging systems at different time steps of the pre-fill and post-fill barrel lubricant coverage testing process according to an exemplary embodiment of the invention. Image **610** is of an empty/pre-fill syringe barrel at time T_0 , image **620** is of a pre-fill barrel containing lubricant on the interior surface of the barrel immediately after spraying with oil at time $T_{e,0}$, image **630** is of a post-fill barrel containing lubricant on the interior surface of the barrel 7 minutes after filling ($T_{f,0}$) with an aqueous-based solution at time $T_{f,0} + 7$ minutes, image **640** is of a post-fill barrel containing lubricant on the interior surface of the barrel 22 minutes after filling ($T_{f,0}$) with an aqueous-based solution at time $T_{f,0} + 22$ minutes, and image **650** is of a post-fill barrel containing lubricant on the interior surface of the barrel 3 days after filling ($T_{f,0}$) with an aqueous-based solution at time $T_{f,0} + 3$ days.

15

FIG. 7 shows according to an exemplary embodiment of the invention images **700** of an empty/pre-fill plastic syringe barrel at time $T_{e,0}$ (without lubricant). Image **510** is a computer-processed version of **512**, which itself is an enlarged version of image **514** obtained from the syringe barrel. The images are homogeneous with alternating dark and light regions caused by the presence of the mask, which is a 10 cm by 10 cm by 1 cm aluminum block with 1 mm straight grooves cut through the aluminum. An edge detection algorithm, the process applied to image **510**, shows a small number of plastic molding

20

defects in the empty barrel, which cause changes in the refractive index.

FIG. 8 shows according to an exemplary embodiment of the invention images **800** of a pre-fill plastic barrel containing lubricant on the interior surface of the barrel immediately after spraying with oil at time $T_{e,0}$. Image **520** is a computer-processed version of **522**, which itself is an enlarged version of image **524** obtained from the syringe barrel. 20 cSt viscosity oil was used for lubrication. The images obtained immediately after spraying with oil, indicate a distribution of oil droplets in the empty barrel. The edges of individual oil droplets are determined using an edge detection algorithm, as shown in image **520**.

FIG. 9 shows according to an exemplary embodiment of the invention images **900** of a post-fill barrel containing lubricant on the interior surface of the barrel 3 minutes after filling ($T_{f,0}$) with an aqueous-based solution at time $T_{f,0} + 3$ minutes. Image **530** is a computer-processed version of **532**, which itself is an enlarged version of image **534** obtained from the syringe barrel. 20 cSt viscosity oil was used for lubrication.

FIG. 10 shows according to an exemplary embodiment of the invention images **1000** of a post-fill barrel containing lubricant on the interior surface of the barrel 9 minutes after filling ($T_{f,0}$) with an aqueous-based solution at time

$T_{f,0} + 9$ minutes. Image **540** is a computer-processed version of **542**, which itself is an enlarged version of image **544** obtained from the syringe barrel. 20 cSt viscosity oil was used for lubrication.

5 The images of the empty plastic barrel after respectively 3 minutes and 9 minutes (**FIGs 9-10**) show that droplet coalescence has already taken place and there is less evidence of individual droplets. In these regions it is not clear whether there is lubricant present since the coalesced droplets have a uniform refractive index and the image becomes similar to **FIG. 7** for the empty plastic
10 barrel.

FIG. 11 shows according to an exemplary embodiment of the invention images **1100** of a post-fill barrel containing lubricant on the interior surface of the barrel 10 minutes after filling ($T_{f,0}$) with an aqueous-based solution at time
15 $T_{f,0} + 10$ minutes. Image **550** is a computer-processed version of **552**, which itself is an enlarged version of image **554** obtained from the syringe barrel. 20 cSt viscosity oil was used for lubrication. An aqueous solution was used for filling. The images show oil beading into droplets after 10 minutes because water and oil are immiscible, verifying the presence of oil in the plastic barrel.

20

FIG. 12 shows according to an exemplary embodiment of the invention images **1200** of an empty/pre-fill glass syringe barrel at time $T_{e,0}$ (without

lubricant). Image **610** is a computer-processed version of **612**, which itself is an enlarged version of image **614** obtained from the syringe barrel. An edge detection algorithm, the process applied on image **610**, shows the presence of defects in the glass as well as external impurities attached to the inside or
5 outside glass wall.

FIG. 13 shows according to an exemplary embodiment of the invention images **1300** of a pre-fill glass barrel containing lubricant on the interior surface of the barrel immediately after spraying with oil at time $T_{e,0}$. Image
10 **620** is a computer-processed version of **622**, which itself is an enlarged version of image **624** obtained from the syringe barrel. 1000 cSt viscosity oil was used for lubrication. The images obtained immediately after spraying with oil, indicate a distribution of oil droplets in the empty barrel. The edges of individual oil droplets are determined using an edge detection algorithm, as
15 shown in image **620**.

FIG. 14 shows according to an exemplary embodiment of the invention images **1400** of a post-fill barrel containing lubricant on the interior surface of the barrel 7 minutes after filling ($T_{f,0}$) with an aqueous-based solution at time
20 $T_{f,0} + 7$ minutes. Image **630** is a computer-processed version of **632**, which itself is an enlarged version of image **634** obtained from the syringe barrel. 1000 cSt viscosity oil was used for lubrication.

FIG. 15 shows according to an exemplary embodiment of the invention images **1500** of a post-fill barrel containing lubricant on the interior surface of the barrel 22 minutes after filling ($T_{f,0}$) with an aqueous-based solution at time **5** $T_{f,0} + 22$ minutes. Image **640** is a computer-processed version of **642**, which itself is an enlarged version of image **644** obtained from the syringe barrel. 1000 cSt viscosity oil was used for lubrication.

The images of the empty glass barrel after respectively 7 minutes and 22 minutes (**FIGs. 14** and **15**) show that droplet coalescence has already taken place and there is less evidence of individual droplets. In these regions it is not clear whether there is lubricant present since the coalesced droplets have a uniform refractive index and the image becomes similar to **FIG. 12** for the empty glass barrel.

15

FIG. 16 shows according to an exemplary embodiment of the invention images **1600** of a post-fill barrel containing lubricant on the interior surface of the barrel 3 days after filling ($T_{f,0}$) with an aqueous-based solution at time $T_{f,0} + 3$ days. Image **650** is an enlarged version of **652**, which itself is an enlarged version of image **654** obtained from the syringe barrel. 1000 cSt viscosity oil was used for lubrication. An aqueous solution was used for filling. The images show oil beading into droplets after 3 days because water and oil are

immiscible, verifying the presence of oil in the glass barrel.

ALGORITHMS: DETECTION AND ANALYSIS

For detection and analysis of the images various techniques can be used as a
5 person skilled in the art would appreciate. For the embodiments presented
herein, a low pass filtering (e.g., Median filter, Gaussian blurring) was applied
to the input sensor image to reduce high-frequency noise. This was followed
by edge detection (e.g., Canny edge detection) to detect features.

10 The detected edge features can then be quantified in a number of ways to
compute quality measures. In general, the one or more pre-fill optical
properties and the one or more post-fill optical properties could be optical
changes related to the applied lubricant, changes in refractive index or optical
features of the lubricant. Examples of quality measures include, but are not
15 limited to:

- Number of features detected per cm^2 ,
- Number of features detected per radial slice,
- Histogram of detected feature sizes, and/or
- Number and sizes of *gaps* (areas containing fewer than some threshold
20 $Thresh_{gaps}$ of features).

Pre-fill and post-fill quality thresholds can be used to accept or reject
respectively the pre-filled lubricant-covered barrel and post-filled lubricant-

covered barrel. Examples of such thresholds include, but are not limited to:

- Accept barrels with an average density d of at least 100000 features/cm² $< d$, reject otherwise,
- 5 • Accept barrels with at least 150000 features/cm² in the first 40% of the barrel (toward the open end) and at least 100000 features/cm² in the remaining 60% of the barrel, reject otherwise,
- Accept barrels where at least 80% of the features are $< 30\text{px}$ (e.g., control on droplet size), reject otherwise, and/or
- Accept barrels with no more than 15% of the barrel being occupied by
10 a *gap* (or area containing fewer than some threshold T_{gaps} of features).

IMPORTANCE OF QUALITY OF TESTING

The teachings and examples provided herein stress the importance of quality testing of the lubrication layer at the inside of the barrel in the pre-filled stage
15 as well as in the post-filled stage, and not just one or the other. As discussed elsewhere herein, failure to perform these quality tests at *both* stages may lead to serious consequences, which could manifest when the syringe is used on patients. Poorly lubricated syringes (e.g., a barrel with very sparse lubrication, or a barrel with 50% of its area covered in gaps), for example, may lead to
20 improper dosing if the injection device stalls in the middle of dosing. Manually pushed devices could also be affected as poor lubrication may require more force to be applied than the physical device can handle, breaking, for instance, the plunger rod.

IMPROVEMENTS

To guarantee or significantly improve high-quality coatings for syringe barrels is through 100%, high-speed inspection of pre-filled *and* post-filled syringes at
5 the time frames specified in this invention, which is clear from the discussions and teachings *herein*.

Simply taking the approach of testing at the pre-filled stage and post-filled stages are let's say time t , where t is the *same time* for both tests would lead to
10 serious problems. For example, for $t = 30$ seconds and η is 20 cSt, the pre-fill test would be timely performed, but the post-fill test would be performed too early, resulting is the wrong conclusion from a quality control standpoint. Similarly, for $t = 15$ minutes and η is 20 cSt, the pre-fill test would be performed too late, and the post-fill test would be timely performed, also
15 resulting is the wrong conclusion from a quality control standpoint.

Furthermore, simply taking one test *or* the other would fail is many different way as the following problems/scenarios could be identified:

- ***Pre-fill accepted incorrectly, no post-fill test.*** The first problem could
20 be that the pre-filled lubricated syringe could have been *accepted incorrectly*, by testing *passed* the specified time pre-fill quality test window, as in fact it should have been *rejected*. Then if there is *no* post-fill quality test, this particular syringe would eventually have been

used for a patient, as in fact it should *not* have been used and been *rejected*.

- ***Pre-fill accepted correctly, but no post-fill test.*** The second problem could be that the pre-filled lubricated syringe could have been
5 *accepted correctly*, and then during the period between lubrication and filling with an aqueous-based solution something could have happened to the lubrication coverage resulting in a coverage below the quality threshold, but then if there is *no* post-fill quality test this particular syringe would have passed on to the patient, *incorrectly* (defined as
10 when there would have been a post-filled quality test, as embodied in this invention).
- ***Pre-fill rejected incorrectly.*** The third problem could be that the pre-filled lubricated syringe could have been *rejected incorrectly*, by testing *passed* the specified pre-fill quality test window, as in fact it
15 should have been *correctly accepted* as a useful syringe.
- ***Pre-fill accepted correctly, post-fill rejected incorrectly.*** The fourth problem could be that the pre-filled lubricated syringe could have been *accepted correctly*. If there is a post-fill quality test, the post-filled lubricated syringe could have been *accepted incorrectly*, by testing
20 *prior* to the specified time post-fill quality test window, as in fact it should have been *rejected*. This syringe would have been *incorrectly passed* on to the patient as a useful syringe.

In alternate embodiment, the invention can be defined as a significant and crucial method and system improvement to the delivery of high-quality lubricant coatings being delivered along a syringe barrel's life. Especially, these improvements are not only significant in view of the current practice, but
5 also these improvements could potentially be reducing health-risk or avoiding life-threatening situations. In view of this, embodiments of the invention could be defined as a quality control method or system for determining a lubricant coverage at the inside surface of a syringe barrel, wherein the significant and crucial improvement comprises either alone or in any
10 combination of the following steps:

- *prior* to filling the lubricant-covered barrel with an aqueous-based solution, obtaining one or more pre-fill optical properties of the lubricant-covered barrel, where the one or more pre-fill optical properties are obtained at a time T_e defined as $T_{e,0} < T_e \leq T_{e,1}$,
15 where $T_{e,0}$ is the time of the applying the lubricant, wherein $T_{e,1} = 0.05\eta$ defined in minutes, where η is a viscosity of the applied lubricant and defined in cSt, and where the one or more pre-fill optical properties are obtain using a first imaging system, and determining a pre-fill quality measure for the lubricant-covered barrel using the one
20 or more pre-fill optical properties as input to a computer-implemented pre-fill barrel quality measure determination program executed on a first computer, where the pre-fill quality measure is used by a first

syringe processing system to reject or accept the lubricant-covered barrel based on a predetermined pre-fill quality threshold.

- *post filling* the syringe barrel with an aqueous-based solution, obtaining one or more post-fill optical properties of the filled lubricant-covered syringe barrel, where the one or more post-fill optical properties are obtained at a time T_f defined as $T_f \geq T_{f,1}$, where $T_{f,1} = 8.8 \exp(0.0063\eta)$ defined in minutes and defined from $T_{f,0}$, where η is the viscosity of the applied lubricant and defined in cSt, where $T_{f,0}$ is the time of the filling the aqueous-based solution, and where the one or more post-fill optical properties are obtained using the first imaging system or a second imaging system, and determining a post-fill quality measure for the filled lubricant-covered barrel using the one or more post-fill optical properties as input to a computer-implemented post-fill barrel quality measure determination program executed on the first computer or a second computer, where the post-fill quality measure is used by the first syringe processing system or a second syringe processing system to reject or accept the filled lubricant-covered barrel based on a predetermined post-fill quality threshold.

APPENDIX

SYRINGE

A medical syringe **1800** is a pump with of a plunger **1810** that fits tightly in a cylindrical glass or plastic tube (called a barrel) **1820**. Plunger **1810** can be
5 pushed (arrow **1830**) along inside cylindrical tube **1820**, allowing the syringe to eject material from the end of the tube **1840**. The open end **1842** of the syringe may be fitted with a hypodermic needle, a nozzle, or tubing **1840** to direct the flow of the material out of the barrel.

10 LUBRICANT APPLICATION

The application of the lubricant using a lubricant covering system is in accordance to Chan et al. (Syringe Siliconization Process Investigation and Optimization. J. Pharm. Sci. and Tech. 2012, 66 136-150). The syringe barrels in the examples in this invention are sprayed with Dow Corning oil,
15 with a viscosity of 20 centistokes (cSt) and in some embodiments 1000 cSt. The volume sprayed was 0.5 μ L with a flow rate of 2.5 slm (standard liter per minute) and nozzle temperature of 65 degrees Celsius. The spray system started dispensing the oil at 30 mm outside of the syringe barrel and stopped at 40 mm inside the syringe barrel. The duration of the spray process is 1
20 second. After the spray process, the syringe barrel is inspected using an imaging system.

IMAGING

The imaging system **1900** image syringe barrel **1910** works together with a backlight **1920**, paired with a light mask **1930** and a camera **1940**. The purpose of mask **1930** is to produce a light pattern **1960** with alternating dark
5 and light regions, which makes it easier to detect changes in the refractive index caused by the coalescing lubricant. An example of a light source that could be employed is a model LED light source. The lens that could be used is a Telecentric Lens with magnification. The camera could be a metal-oxide-semiconductor (CMOS or CCD). To capture images an exposure time of 2
10 milliseconds could be used.

CLAIMS

What is claimed is:

1. A quality control method for determining a lubricant coverage at the inside surface of a syringe barrel for a pre-filled and post-filled syringe barrel, wherein the pre-filled syringe barrel is defined as prior/pre to a time of filling of the syringe barrel with an aqueous-based solution, and wherein the post-filled syringe barrel is defined as after/post a time of the filling of the syringe barrel with an aqueous-based solution, comprising:
 - for the pre-filled syringe barrel:
 - (a) providing a pre-filled syringe barrel having an inner surface, wherein the inner surface has not yet been covered with a lubricant;
 - (b) applying a lubricant to cover to the inner surface of the pre-filled syringe barrel using a lubricant covering device, therewith creating a lubricant-covered pre-filled syringe barrel;
 - (c) prior to filling the lubricant-covered pre-filled syringe barrel with an aqueous-based solution, obtaining one or more pre-fill optical properties of the lubricant-covered barrel, wherein the one or more pre-fill optical properties are obtained at a time T_e defined as

$$T_{e,0} < T_e \leq T_{e,1}$$
 wherein $T_{e,0}$ is the time of the applying the lubricant, wherein

$$T_{e,1} = 0.05\eta$$

defined in minutes, wherein η is a viscosity of the applied lubricant and defined in cSt, and wherein the one or more pre-fill optical properties are obtain using a first imaging system;

- 5 (d) determining a pre-fill quality measure for the lubricant-covered pre-filled syringe barrel using the one or more pre-fill optical properties as input to a computer-implemented pre-fill barrel quality measure determination program executed on a first computer, wherein the pre-fill quality measure is used by a first
10 syringe processing system to reject or accept the lubricant-covered pre-filled syringe barrel based on a predetermined pre-fill quality threshold; and

for the post-filled syringe barrel:

- (e) providing a pre-filled lubricant-covered syringe barrel, wherein the
15 pre-filled lubricant-covered syringe barrel has not yet been filled with the aqueous-based solution;
- (f) filling the pre-filled lubricant-covered syringe barrel with an aqueous-based solution using an aqueous-based solution filling device, therewith creating a lubricant-covered post-filled syringe
20 barrel;
- (g) obtaining one or more post-fill optical properties of the lubricant-covered post-filled syringe barrel, wherein the one or more post-fill optical properties are obtained at a time T_f defined as

$$T_f \geq T_{f,1},$$

wherein

$$T_{f,1} = 8.8 \exp(0.0063\eta)$$

defined in minutes and defined from $T_{f,0}$, where η is the viscosity

5 of the applied lubricant and defined in cSt, wherein $T_{f,0}$ is the time of the filling the aqueous-based solution, and wherein the one or more post-fill optical properties are obtained using the first imaging system or a second imaging system; and

(h) determining a post-fill quality measure for the lubricant-covered
10 post-filled syringe barrel using the one or more post-fill optical properties as input to a computer-implemented post-fill barrel quality measure determination program executed on the first computer or a second computer, wherein the post-fill quality measure is used by the first syringe processing system or a second
15 syringe processing system to reject or accept the post-filled lubricant-covered barrel based on a predetermined post-fill quality threshold.

2. The quality control method as set forth in claim 1, wherein the one
20 or more pre-fill optical properties and the one or more post-fill optical properties are optical changes related to the applied

lubricant, changes in refractive index or optical features of the lubricant.

3. The quality control method as set forth in claim 1, wherein the aqueous-based solution is an aqueous-based drug-containing solution.
4. A quality control system for determining a lubricant coverage at the inside surface of a syringe barrel for a pre-filled and post-filled syringe barrel, wherein the pre-filled syringe barrel is defined as prior/pre to a time of filling of the syringe barrel with an aqueous-based solution, and wherein the post-filled syringe barrel is defined as after/post a time of the filling of the syringe barrel with an aqueous-based solution, comprising:
- a pre-fill syringe barrel quality testing sub-system with:
- (a) a lubricant covering device for applying a lubricant to cover an inner surface of the pre-filled syringe barrel, therewith creating a lubricant-covered pre-filled syringe barrel;
 - (b) a first imaging system for obtaining one or more pre-fill optical properties of the lubricant-covered pre-filled syringe barrel, prior to filling the lubricant-covered pre-filled syringe barrel with an aqueous-based solution, wherein the one or more pre-fill optical properties are obtained at a time T_e defined as

$$T_{e,0} < T_e \leq T_{e,1}$$

wherein $T_{e,0}$ is the time of the applying the lubricant, wherein

$$T_{e,1} = 0.05\eta$$

defined in minutes, and wherein η is a viscosity of the applied
lubricant and defined in cSt;

(c) a computer-implemented pre-fill barrel quality measure
determination program executed on a first computer for
determining a pre-fill quality measure for the lubricant-covered
pre-filled syringe barrel using the one or more pre-fill optical
properties as input;

d) a first syringe processing system configured for rejecting or
accepting the lubricant-covered pre-filled syringe barrel based on a
predetermined pre-fill quality threshold and the pre-fill quality
measure; and

a post-fill syringe barrel quality testing sub-system with:

(e) an aqueous-based solution filling device for filling the lubricant-
covered pre-filled syringe barrel with an aqueous-based solution,
therewith creating a lubricant-covered post-filled syringe barrel;

(f) the first imaging system or a second imaging system for obtaining
one or more post-fill optical properties of the lubricant-covered
post-filled syringe barrel, wherein the one or more post-fill optical
properties are obtained at a time T_f defined as

$$T_f \geq T_{f,1},$$

wherein

$$T_{f,1} = 8.8 \exp(0.0063\eta)$$

defined in minutes and defined from $T_{f,0}$, where η is the viscosity

5 of the applied lubricant and defined in cSt, and wherein $T_{f,0}$ is the time of the filling the aqueous-based solution; and

- (g) a computer-implemented post-fill barrel quality measure determination program executed on the first computer or a second computer for determining a post-fill quality measure for the lubricant-covered post-filled syringe barrel using the one or more post-fill optical properties as input; and
- 10
- (h) the first syringe processing system or a second syringe processing system configured for rejecting or accepting the lubricant-covered post-filled syringe barrel based on a predetermined post-fill quality threshold and the post-fill quality measure.
- 15

5. The quality control system as set forth in claim 4, wherein the one or more pre-fill optical properties and the one or more post-fill optical properties are optical changes related to the applied lubricant, changes in refractive index or optical features of the lubricant.
- 20

6. The quality control system as set forth in claim 4, wherein the aqueous-based solution is an aqueous-based drug-containing solution.

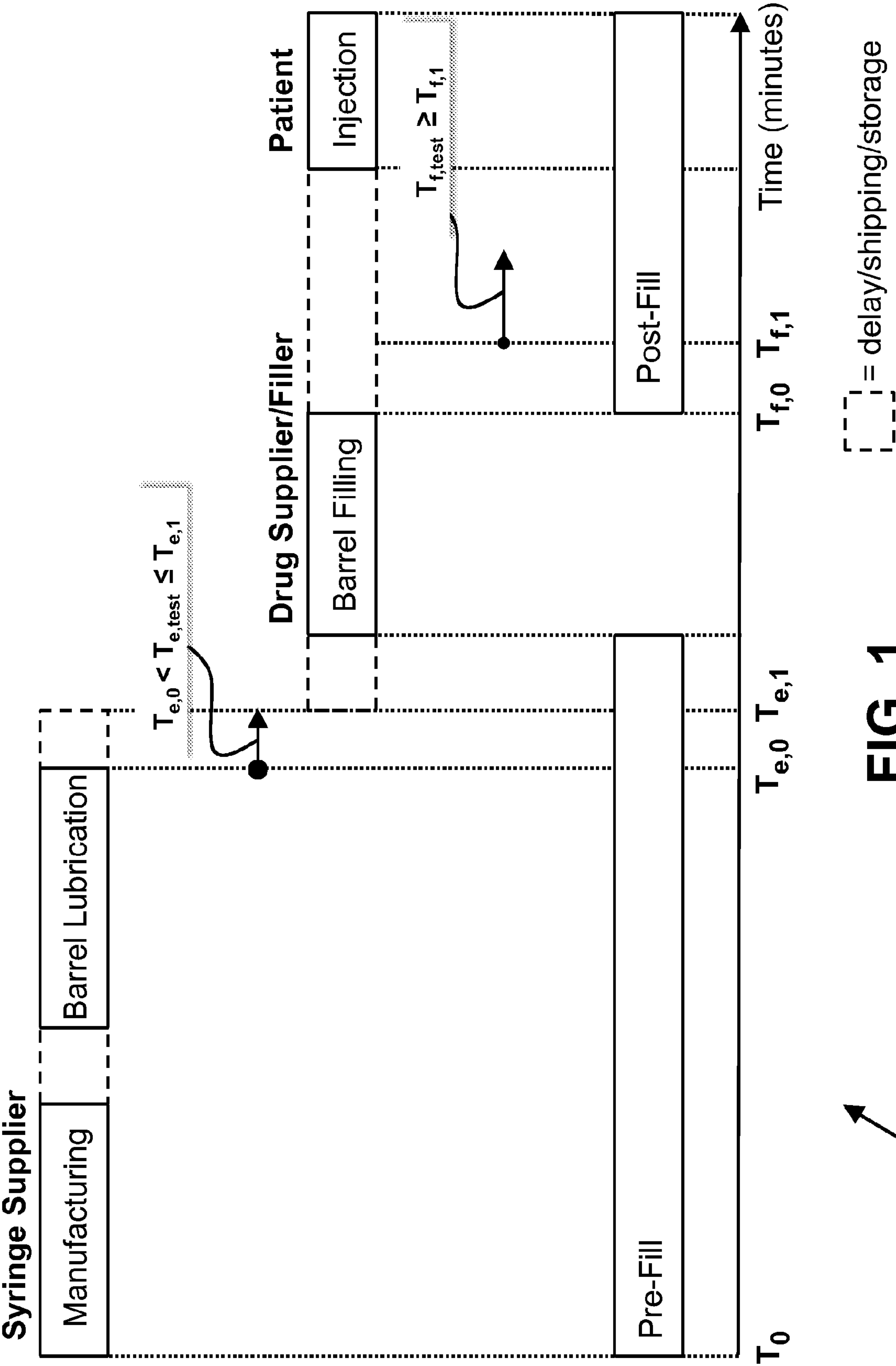
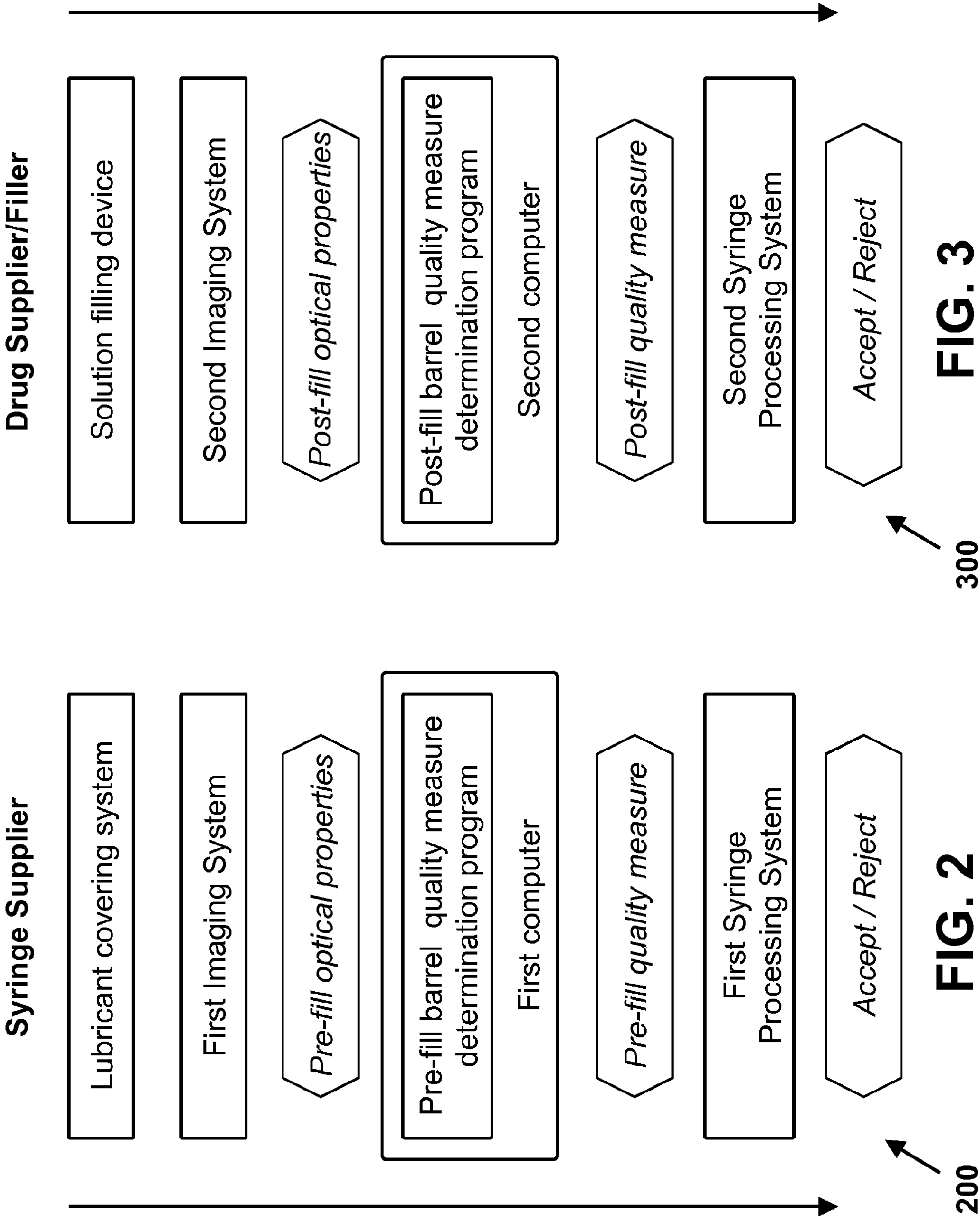


FIG. 1



Syringe Supplier and/or Drug Supplier/Filler

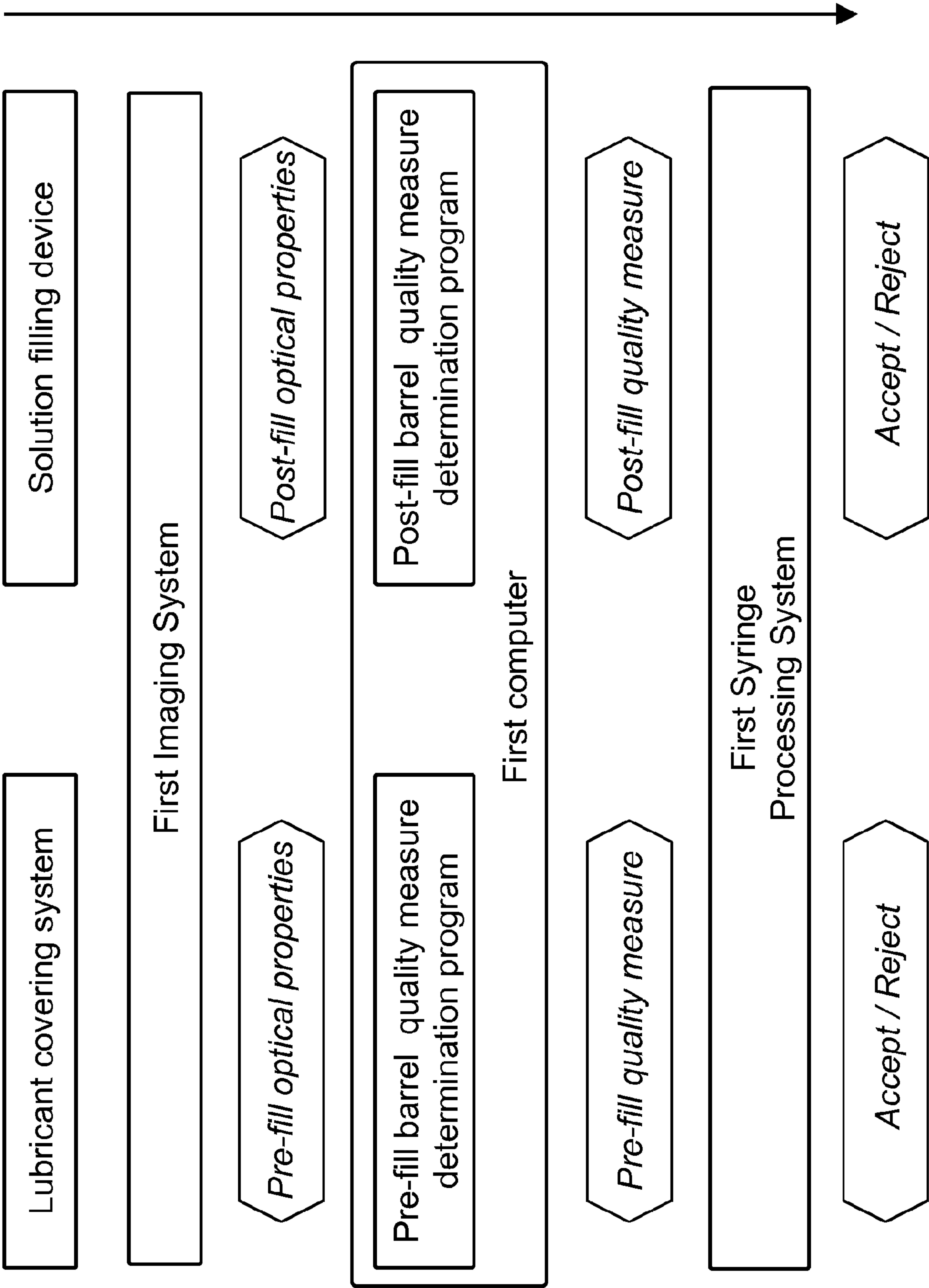
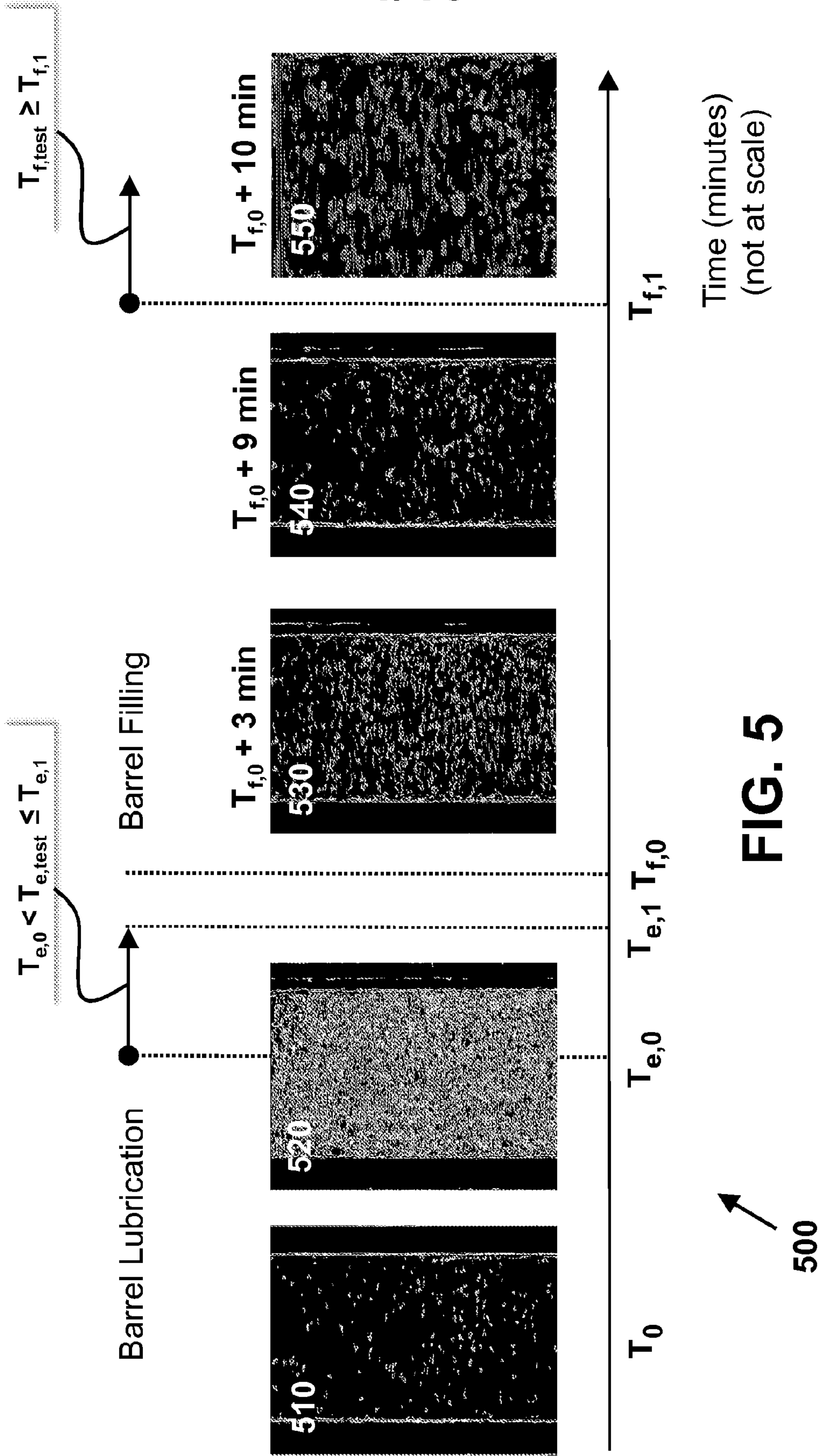


FIG. 4

Plastic Syringe Barrel



Glass Syringe Barrel

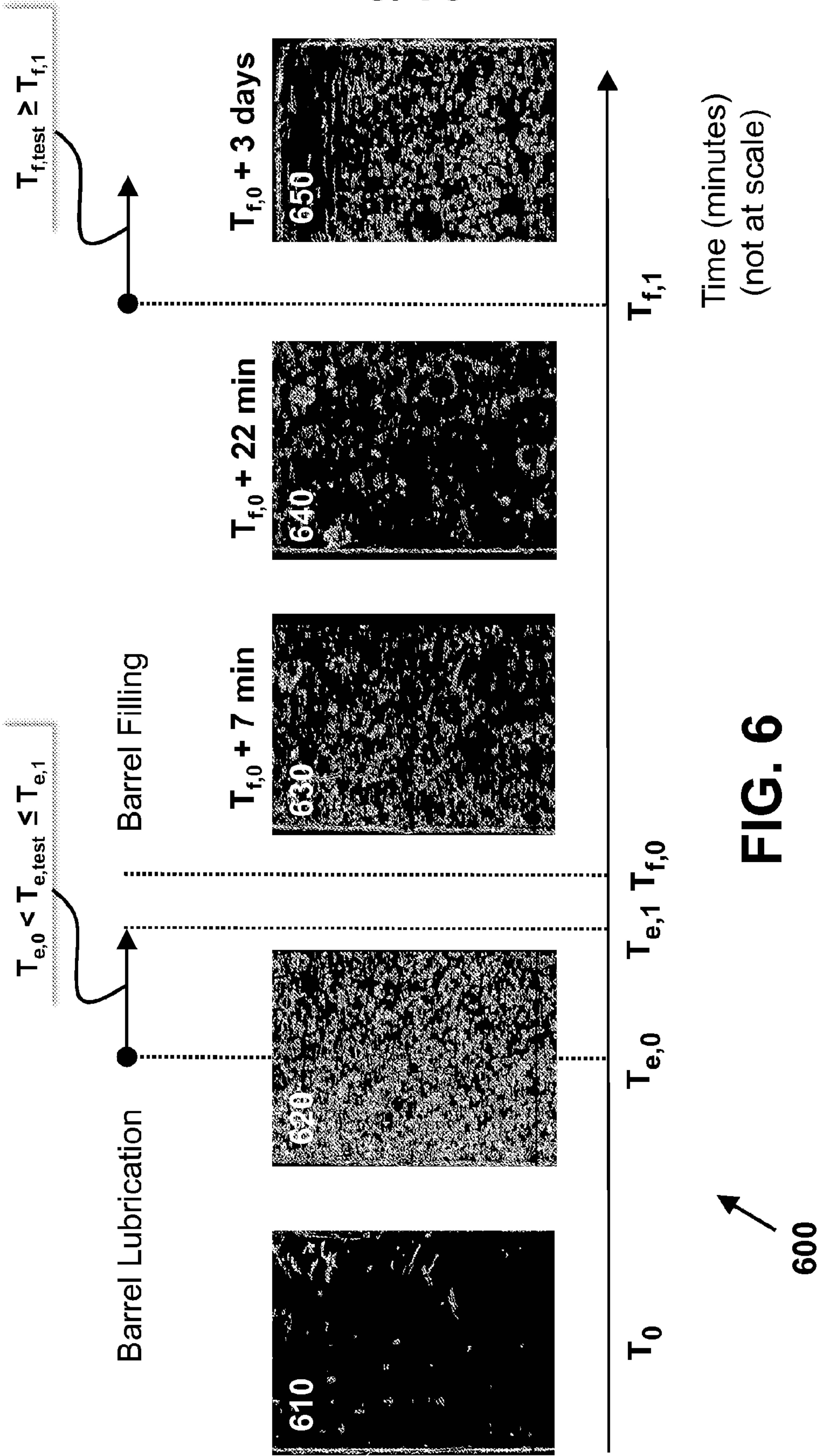
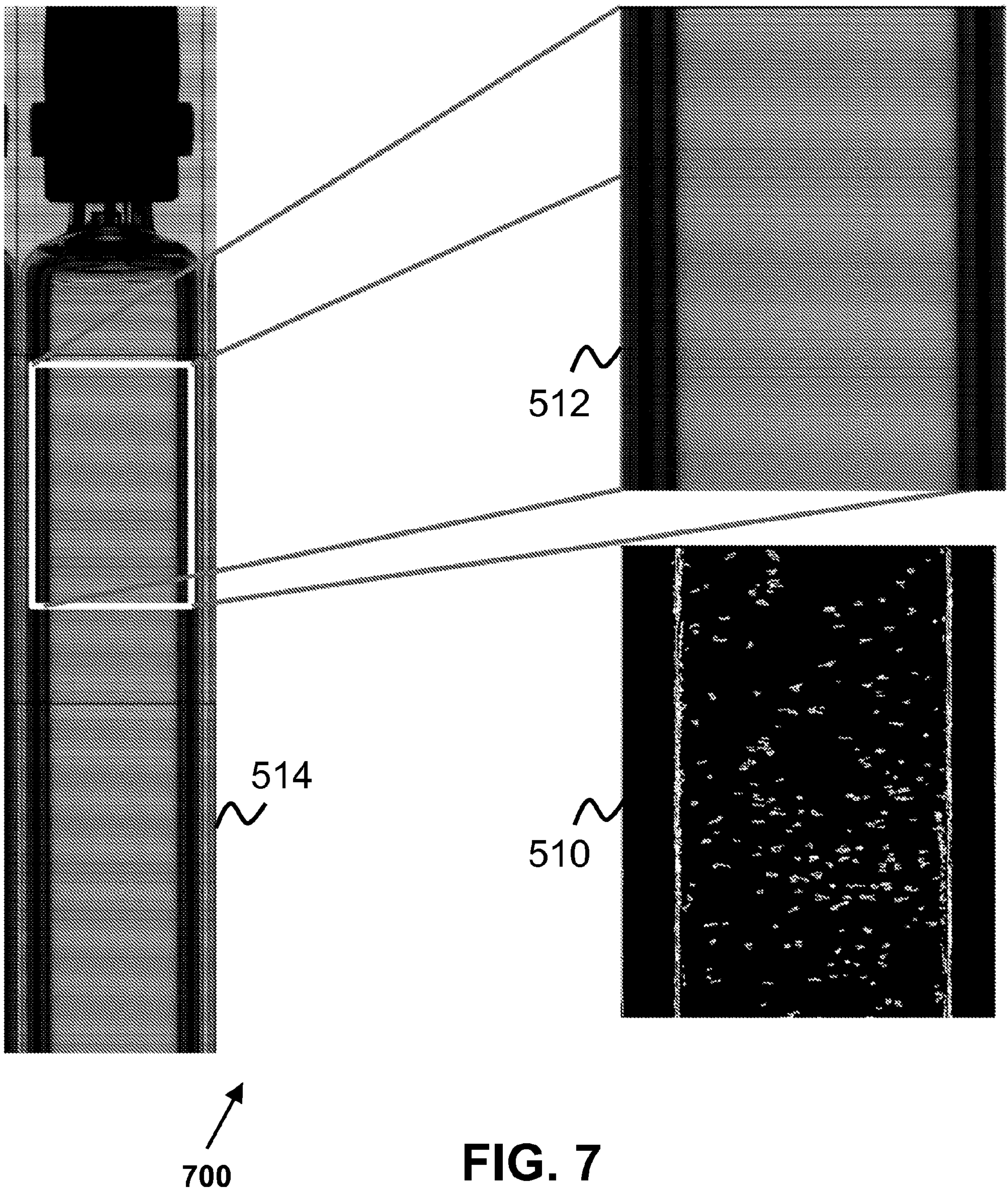


FIG. 6

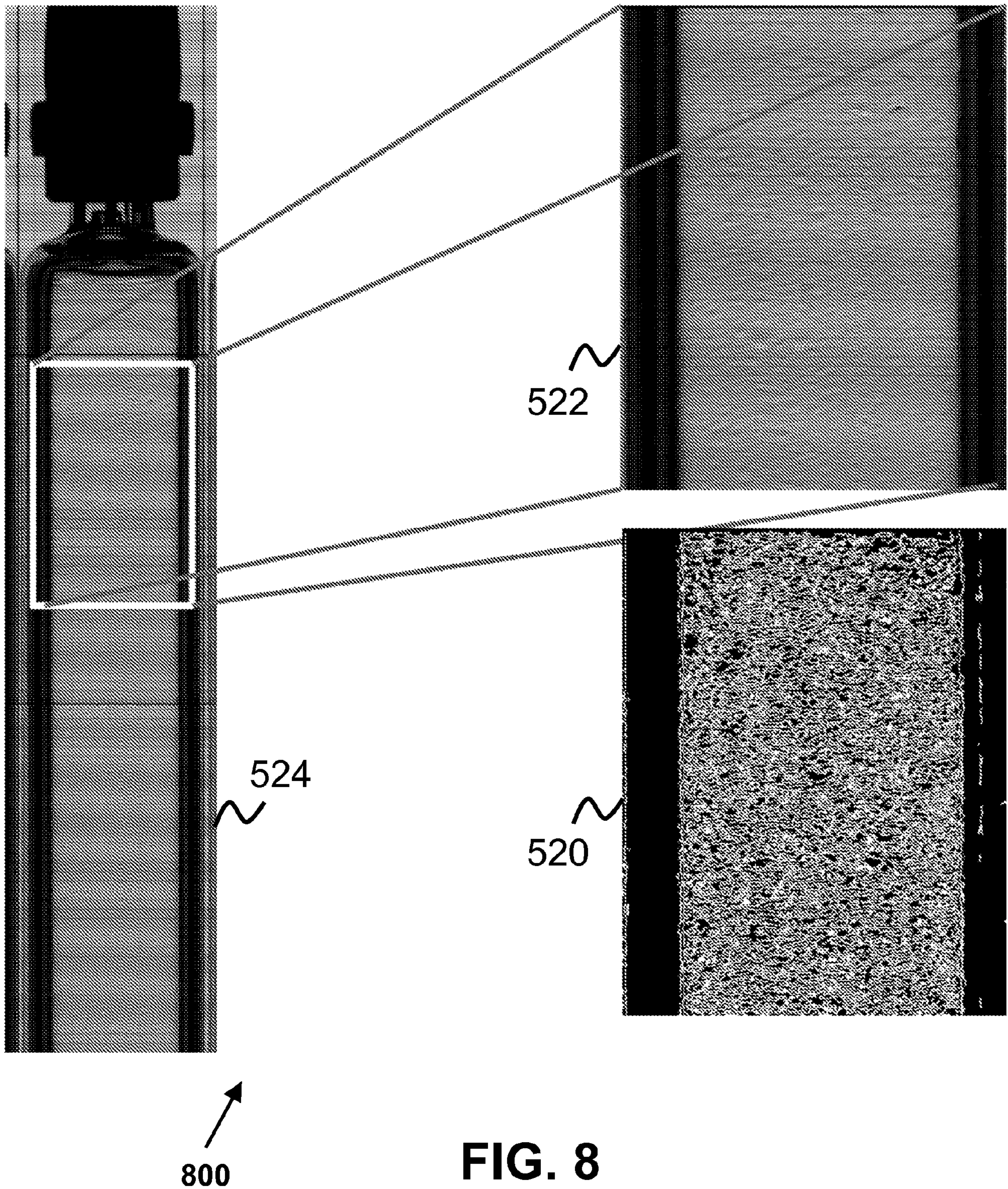
6/18

Plastic Syringe Barrel



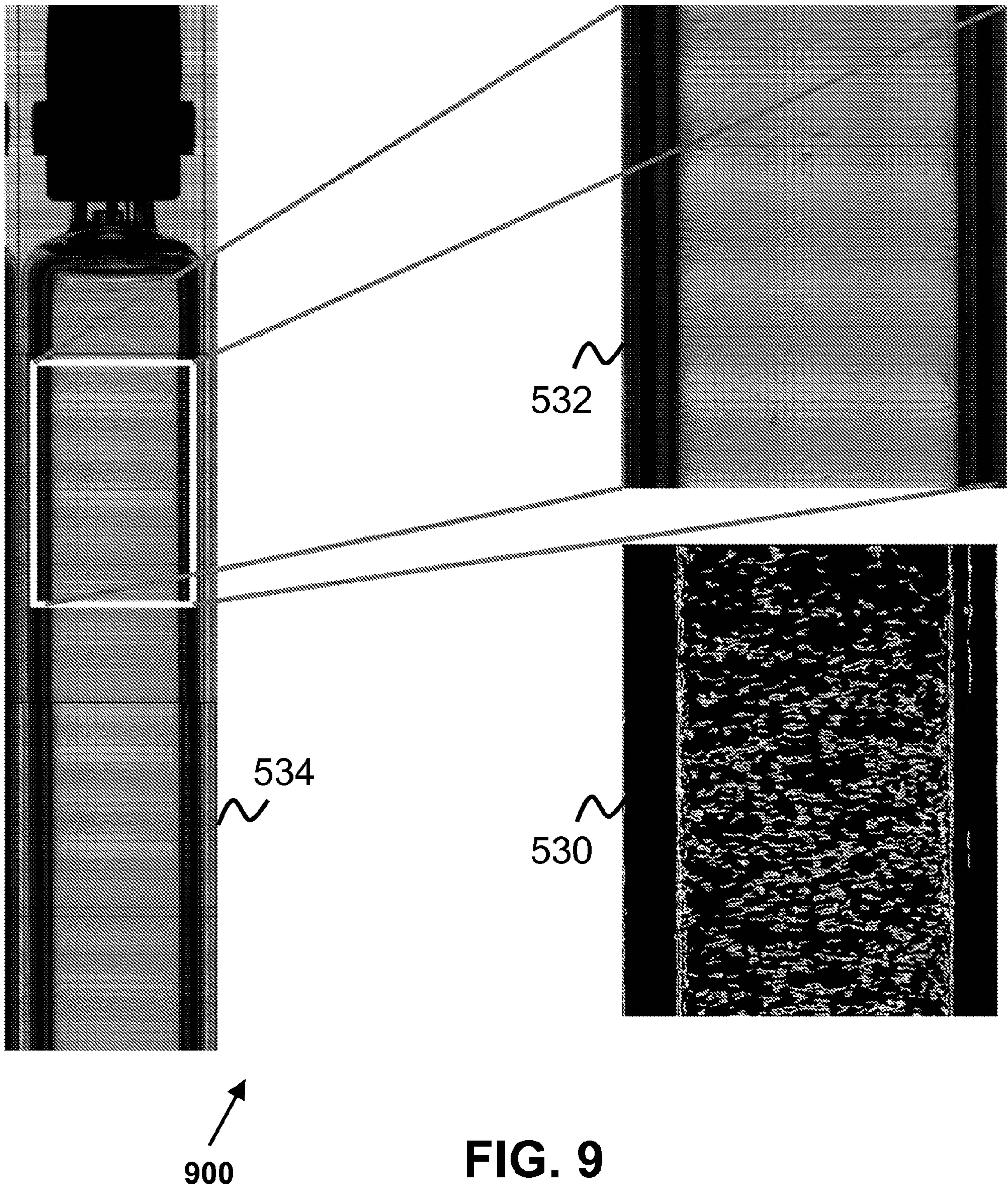
7/18

Plastic Syringe Barrel



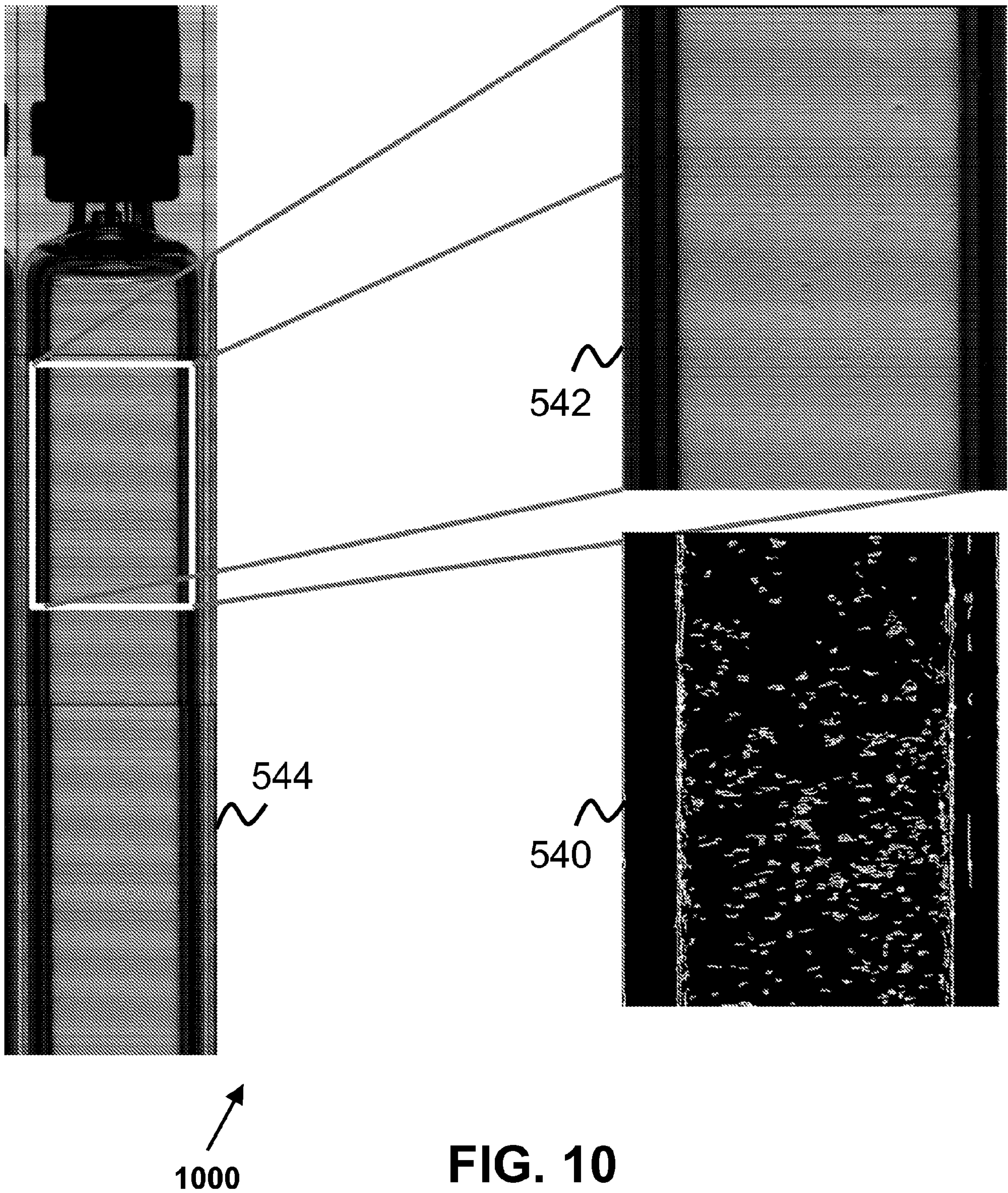
8/18

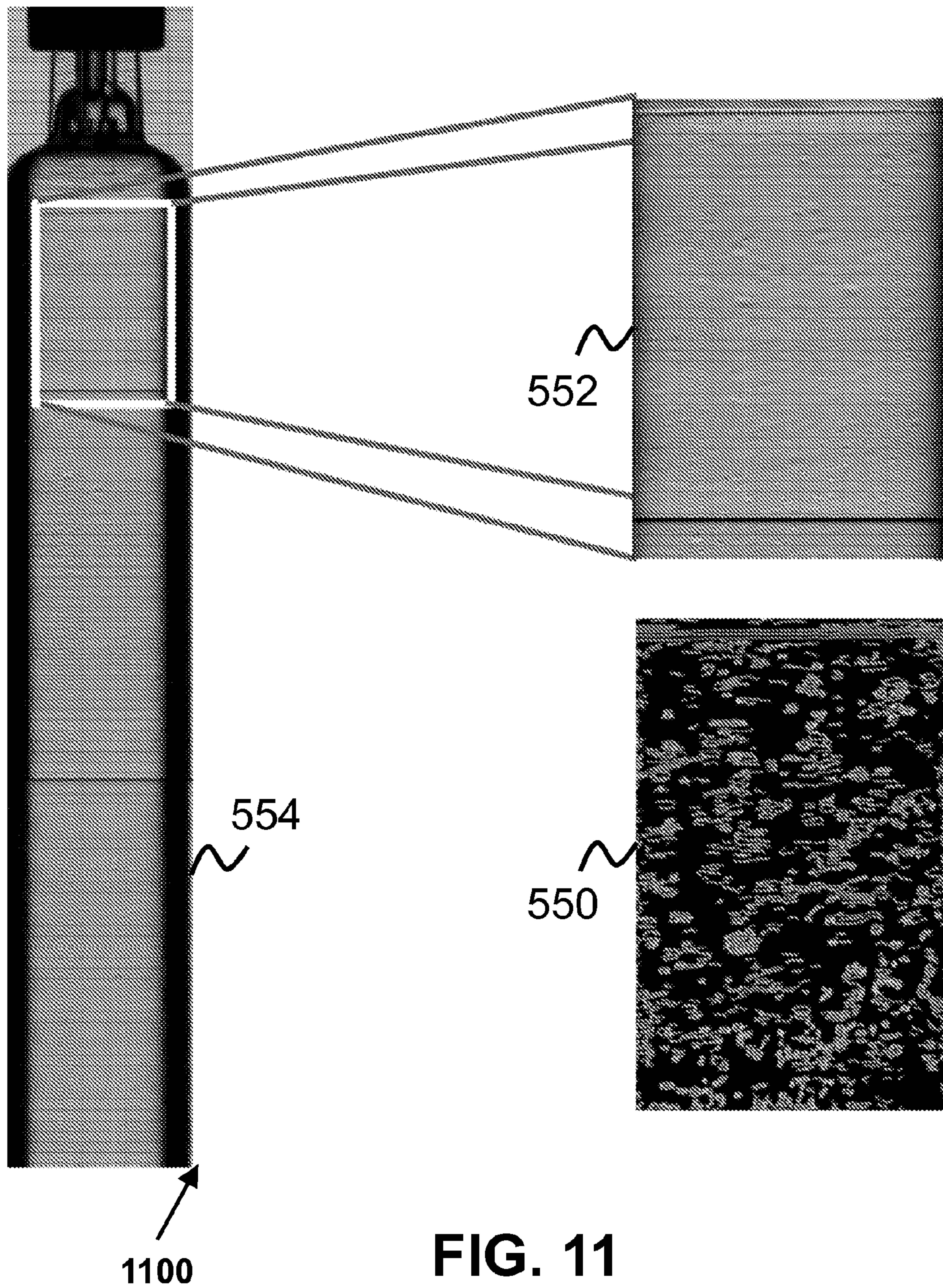
Plastic Syringe Barrel



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Plastic Syringe Barrel



10/18**Plastic Syringe Barrel**

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Glass Syringe Barrel

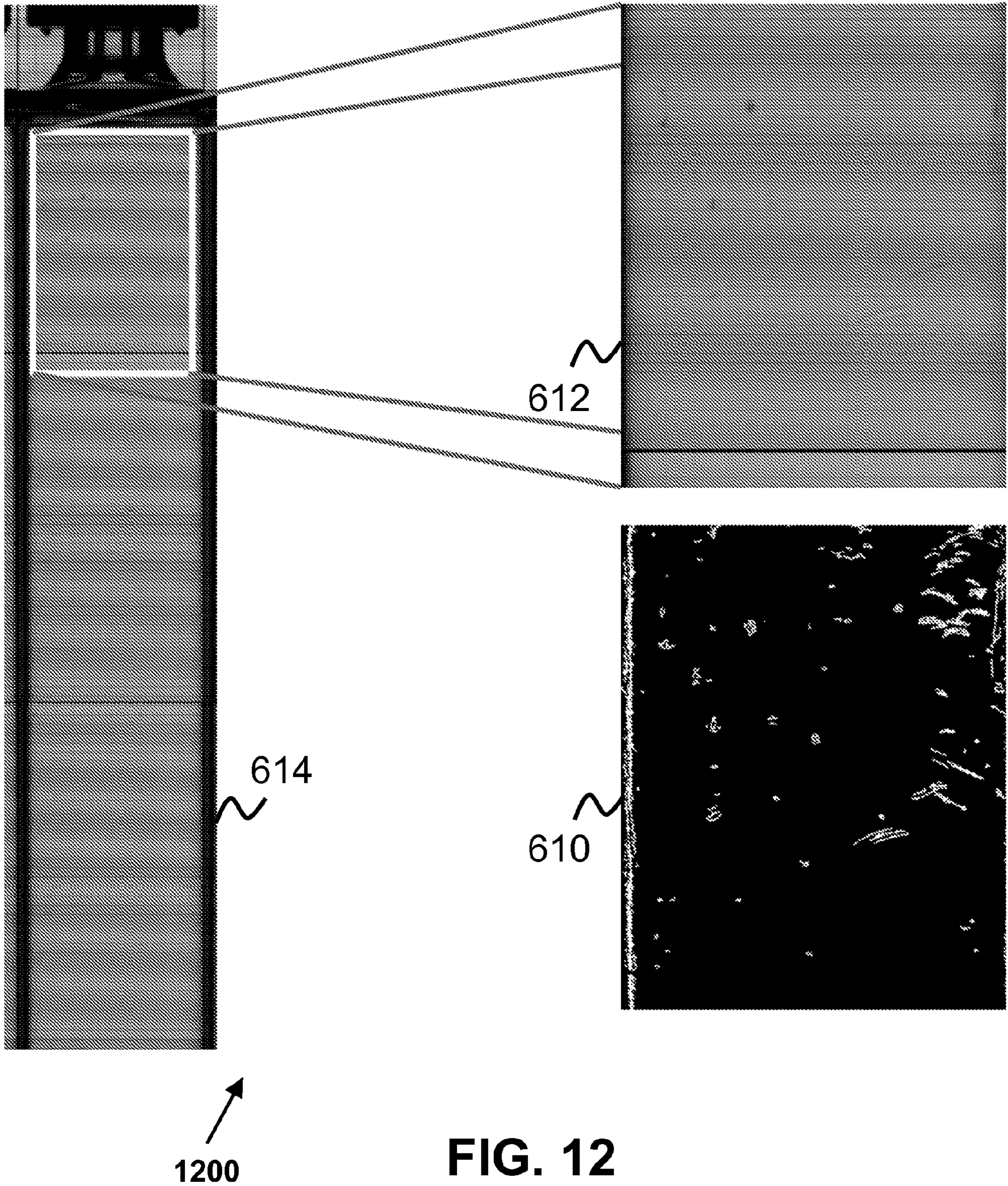


FIG. 12

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Glass Syringe Barrel

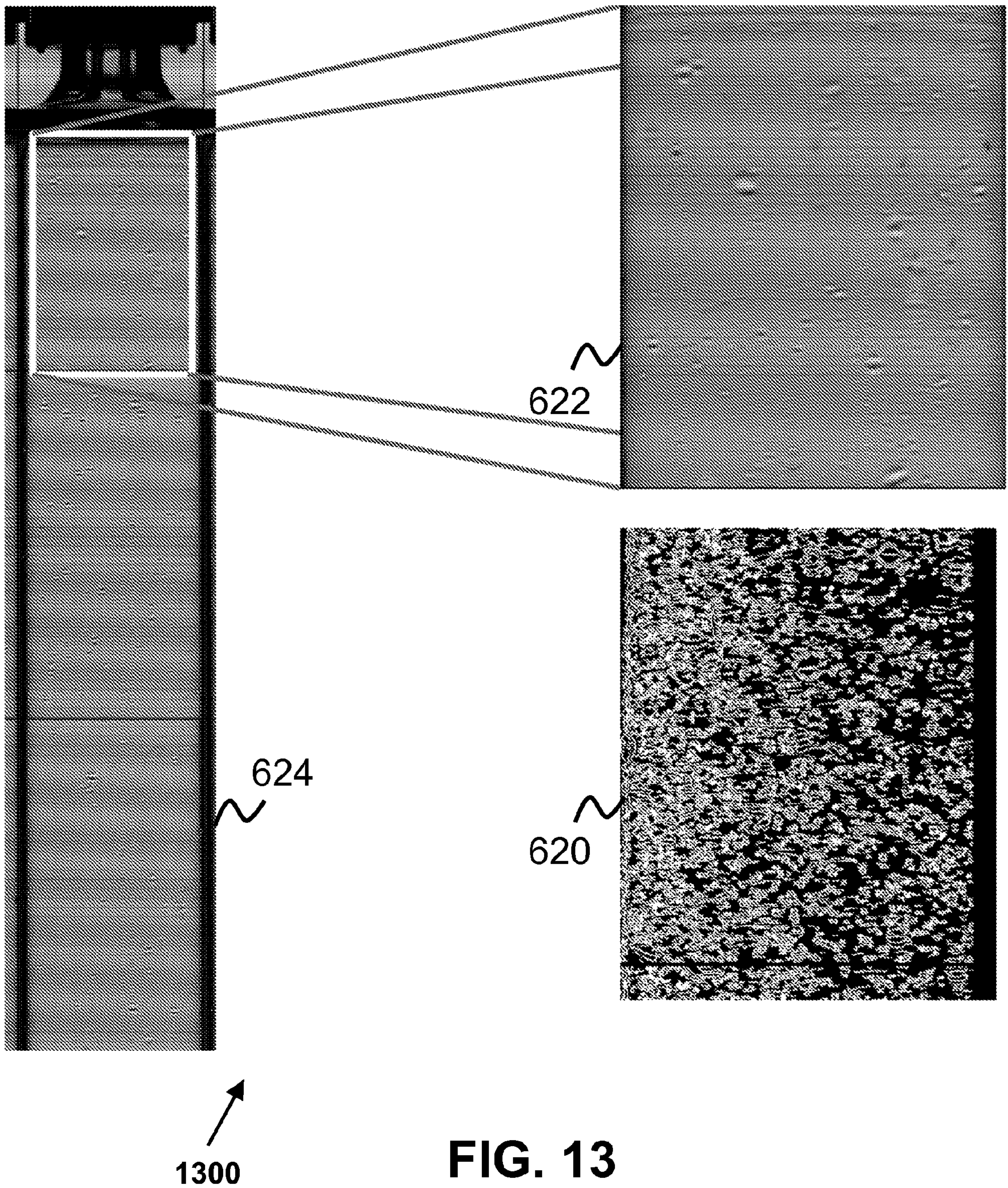
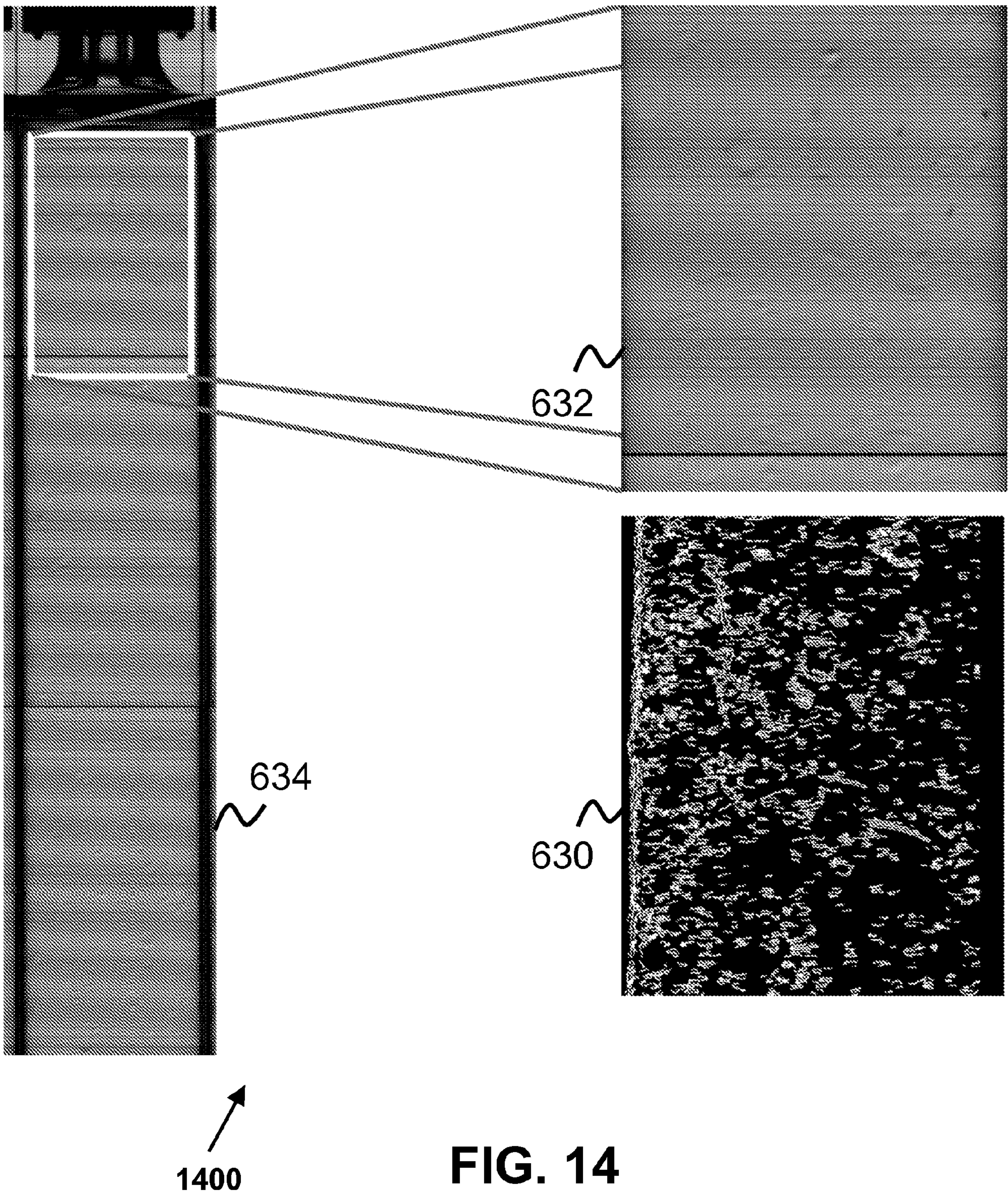


FIG. 13

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Glass Syringe Barrel



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Glass Syringe Barrel

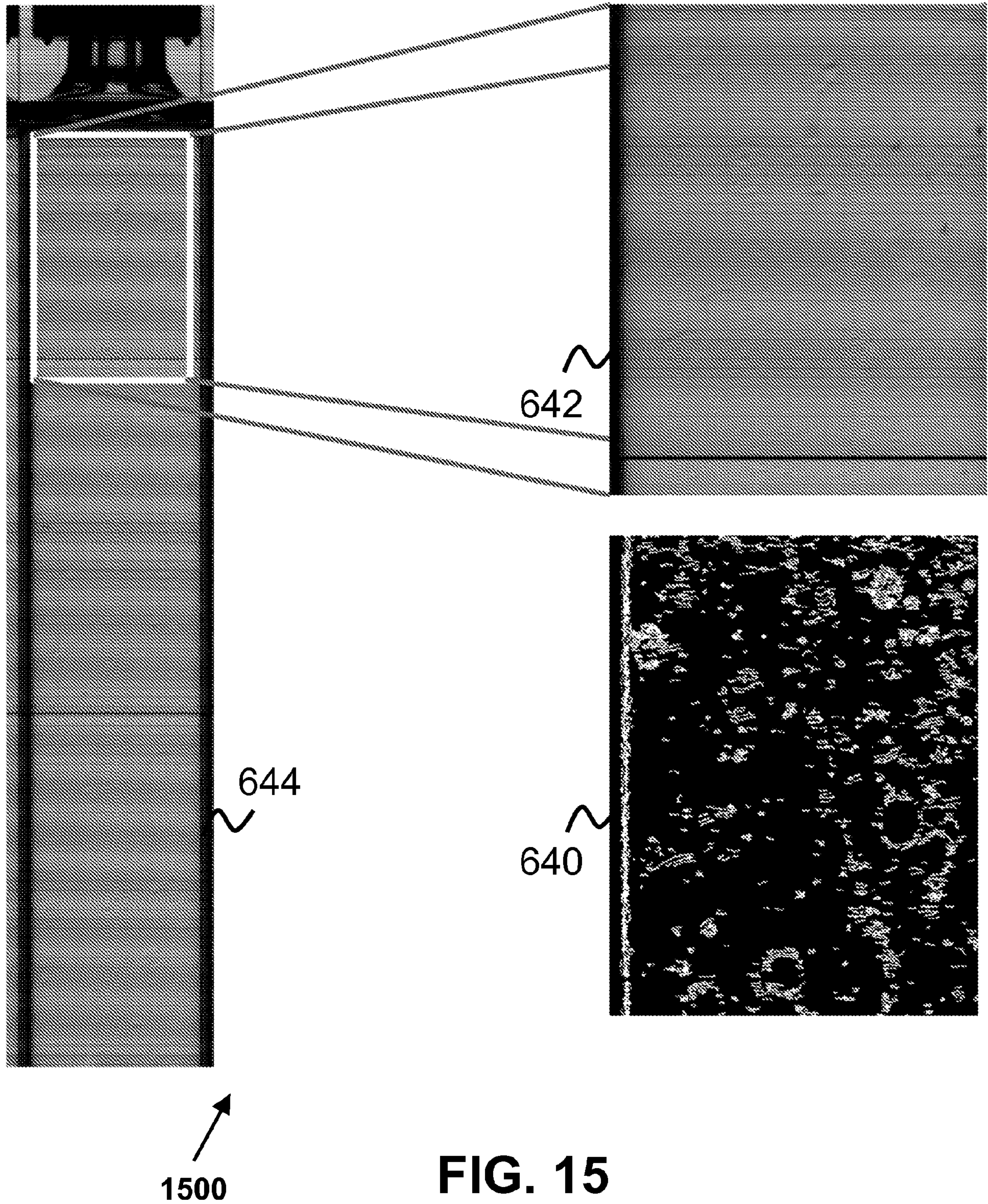
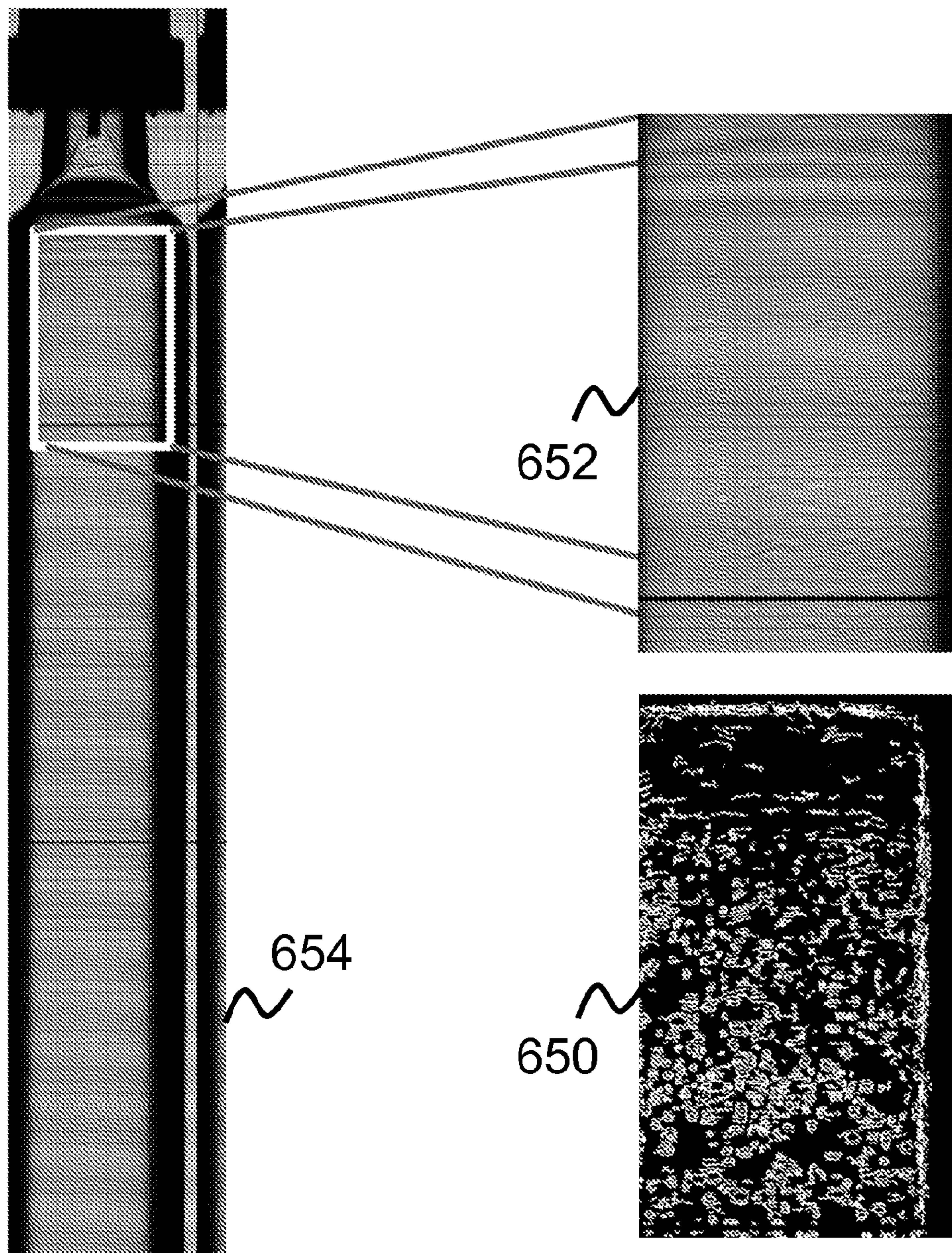


FIG. 15

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Glass Syringe Barrel



1600

FIG. 16

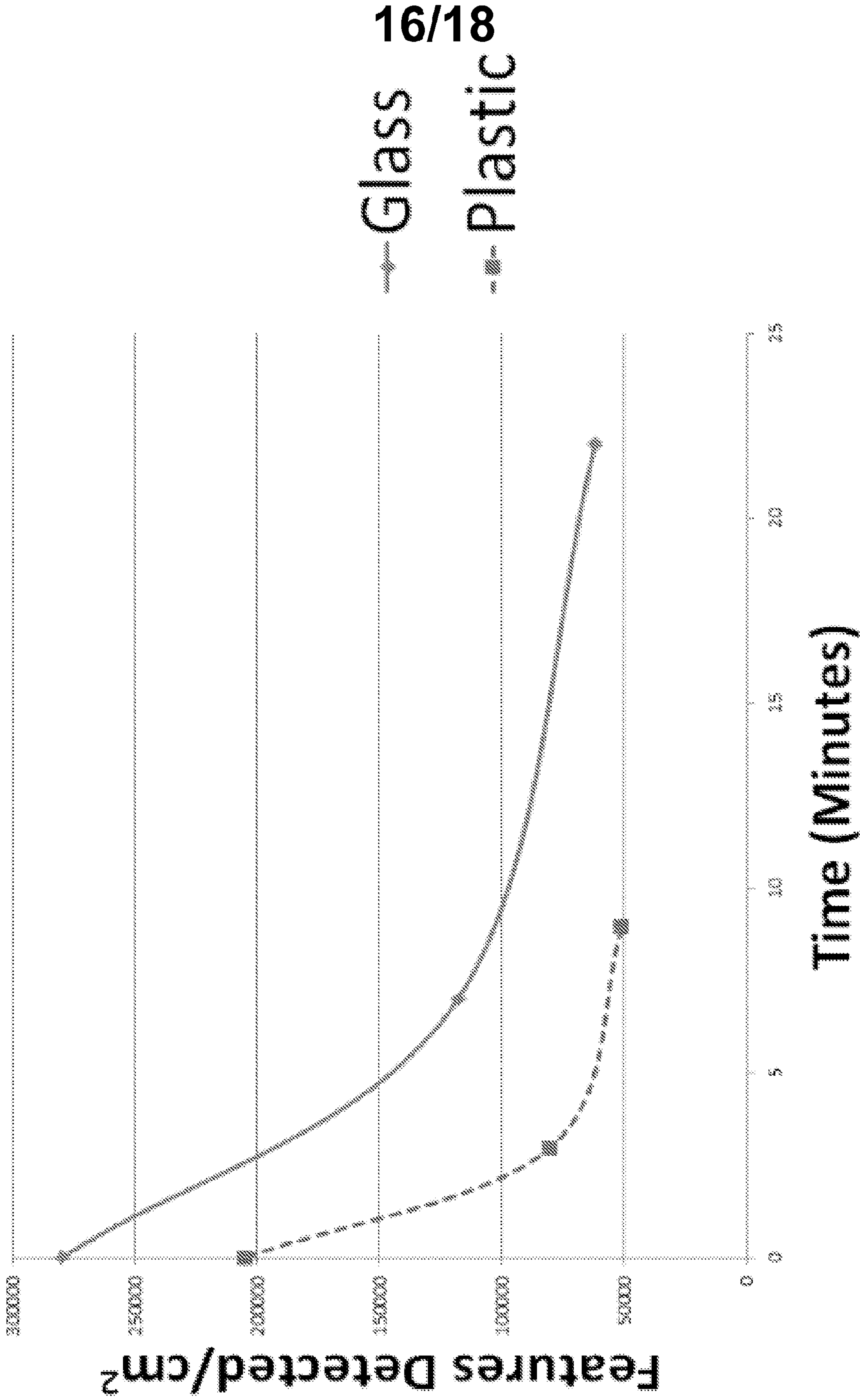


FIG. 17

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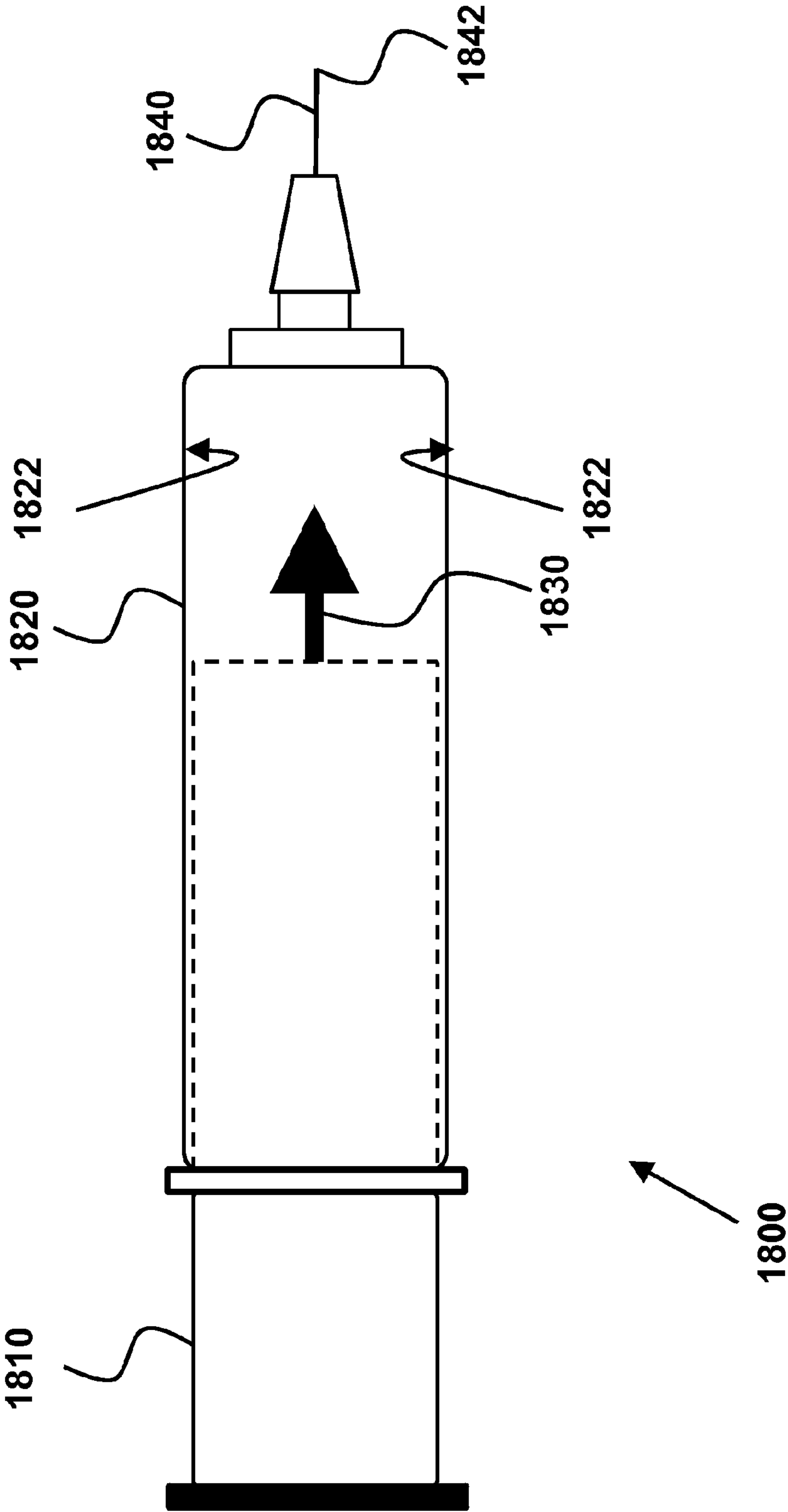


FIG. 18

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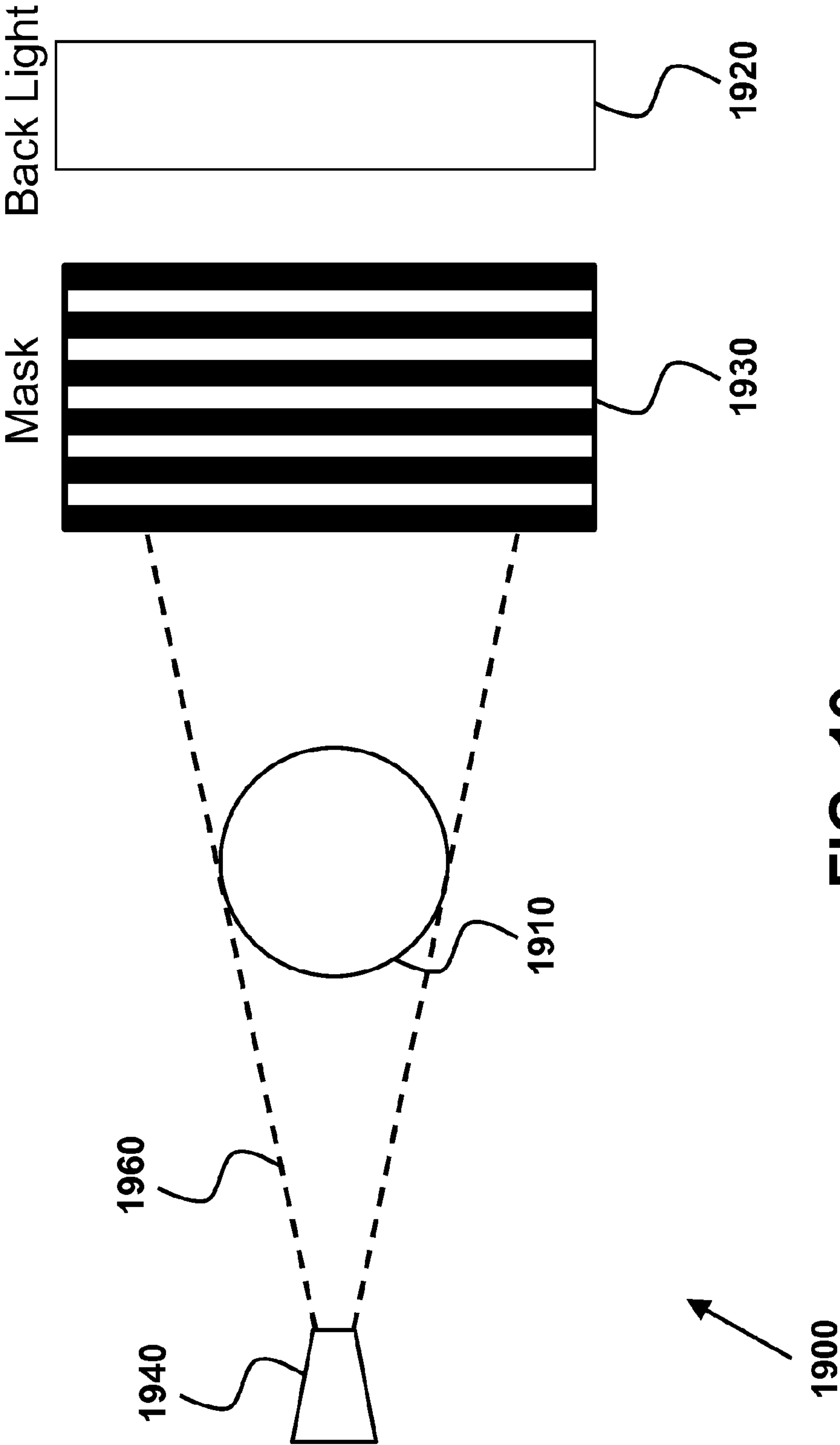


FIG. 19

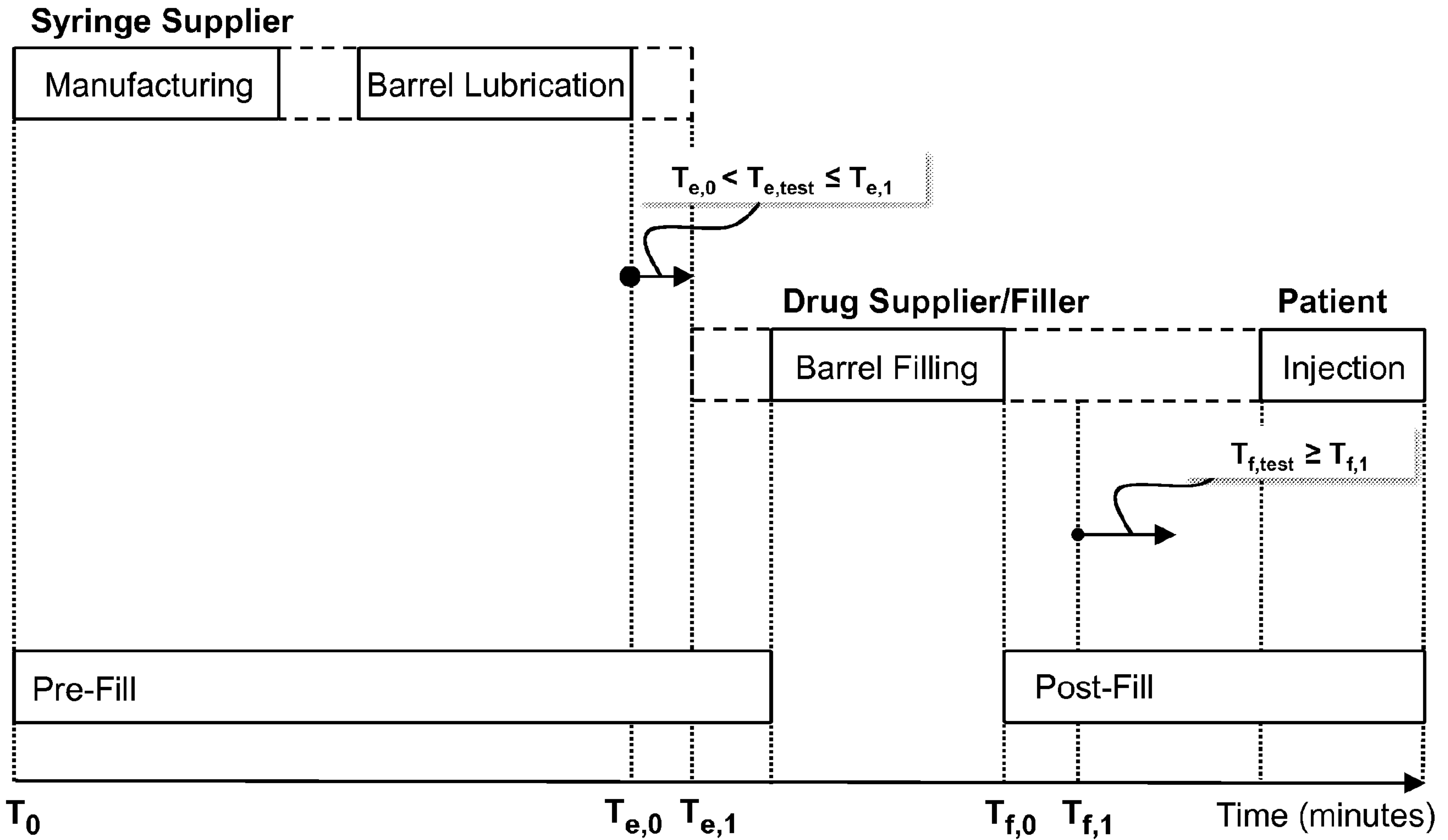


FIG. 1

 = delay/shipping/storage