ensure and promote the growth and development of the science and art of medicine and for the better preservation of the health and lives of the people.

And when this is done, then the old-fashioned pharmacy and the old-fashioned pharmacist will again come into their own. God speed the day!

MANUFACTURE OF AMPOULES.*

BY CHARLES L. BARTHEN.

The methods as well as the advantages of administering medicinal remedies, hypodermically, by means of Hypodermic Tablets, Biological Serums, Antitoxins, etc., are well known. But "ampoules" which are hermetically sealed, glass bulbs, containing standardized and sterile, aqueous or oil solutions of drugs or medicinal chemicals, are considered as comparatively new products on the North American market, although they have been in very common use in Europe and South America for a great many years.

With but very few exceptions the content of ampoules are specifically intended for subcutaneous, intramuscular or intravenous injections; therefore possess all the advantages that hypodermic administration affords.

There are, however, three paramount advantages to be gained by the use of ampoules; namely, convenience, accuracy of dose and the ready to use sterile product.

In view of the facts I have just stated, it is reasonable to expect, that the greatest care, accuracy and aseptic conditions should be observed in the manufacture of ampoules, so that even the most exacting physicians will not hesitate to use them.

I shall endeavor to outline in detail the manner in which ampoules are manufactured in the Laboratory where I am employed.

Manufacturing and Filling of Solutions.—Ampoule solutions with very few exceptions do not contain any material other than the actual medicament and the solvent. The solutions must be neutral in reaction or as near neutral as possible, so that when injected they will not cause any irritation, pain or shock. Therefore they are standardized by chemical tests and assays. As a demonstration I will cite a few examples. Sodium Cacodylate solutions must be very faintly alkaline, and free from Cacodyl, the ester of Cacodylic Acid, which is objectionable. Alkaloidal solutions, such as Quinine, Morphine, Atropine, Strychnine, Emetine, etc., must be faintly acid. Solutions of iron salts must be neutral. Solutions of Adrenalin, Pituitrin, Ergot, Strophanthus, and similar products, are submitted to a physiological assay. Mercurial compounds contain some local anesthetic, because there is no other means of preventing them from causing pain, without changing their very nature.

Filtering.—The solutions are filtered first through paper, then through a Berkefeld or Pasteur filter, the latter preferably because it is more dense. The solutions are forced through the filters with compressed air, and the filtrate received in sterilized bottles. Bacteriologists claim that the solution as it leaves the Pasteur filter is sterile.

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* Read before Detroit Branch A. Ph. A., April meeting, 1918.

Empty Ampoules.—The empty ampoules are made from thoroughly annealed and alkali-free glass tubing. If the glass were not thoroughly annealed, the ampoules would not only be brittle but would crack and break when heated at the high temperature which is necessary to sterilize them. If the ampoules were not made of alkali-free glass, the excess alkali would cause the precipitation, in time if not immediately, of a great many drugs or chemicals from neutral or faintly acid solutions. This is especially true of the alkaloids and iron compounds. In the case of Adrenalin and Pituitrin, complete decomposition takes place in a very short time if there is the slightest excess of alkali present.

The test which we apply to determine the alkalinity of the glass is as follows: The ampoules are filled with a neutral phenolphthalein solution and sealed, then placed in a steam bath and heated until the solution assumes a pink tint, noting the time it requires for this reaction to take place. Some ampoules will cause the solution to turn pink immediately and others will have no effect on the solution after heating for 24 hours. We do not accept any glass that will not meet a test of three to five hours.

The tubing is thoroughly washed and dried, and the ampoules are made with the stems sealed, thus preventing any dust, etc., from getting inside of them. The empty ampoules are sterilized with dry heat at a temperature of 160° C., for one hour, allowed to cool, and just before filling the sealed end of the stem is cut off.

Filling of Ampoules.—Before a process or method of manufacture of a new product can be perfected a considerable amount of experimenting has to be done. This has certainly been true of ampoules. Without a doubt the greatest difficulty encountered in the manufacture of ampoules, has been to obtain a suitable and efficient method of filling each and every ampoule, with an accurately measured amount of clear and sterile solution. You can take a hypodermic syringe, draw in a definite amount of solution and expel it into an ampoule; this is an accurate but very expensive way, or you may fill ampoules by means of a burette, but the success of this method depends entirely upon the eye and accuracy of the operator. After constantly experimenting for years, we have adopted machines that put exactly the amount of solution we desire into each ampoule; these machines fill from 25 to 35 ampoules a minute. The ampoules are then sealed by means of a blast lamp, the heat of which softens the glass, and the edges of the stems are welded together into a solid mass, making a hermetic seal. After filling there always remains, in the stems, a very small amount of solution, which sometimes causes considerable trouble when the ampoules are sealed, particularly with solutions of Caffeine and Sodium Benzoate, and Sodium Cacodylate. These salts when heated with the glass combine with it, making the tip of the ampoule so brittle that the slightest jar will cause it to crumble or fall off. In the case of Quinine Salts the intense heat causes the Quinine to char, so that when the ampoule is agitated, you will notice small specks of charcoal suspended in the solution.

To obviate the troubles just mentioned we wash down this liquid with a little distilled water.

Sterilizing after Filling.—In spite of all the precautionary methods we may adopt in order to maintain aseptic conditions while handling the solutions, apparatus and ampoules, there is a possibility of the solution becoming contaminated

with bacteria. To insure the sterility of the product, the ampoules after filling and sealing, are placed in sheet metal boxes, the top and bottom of which are made of metal screening, and then sterilized by means of steam or hot water, at a temperature the product will permit, for 15 minutes to 1 hour, on each of 3 consecutive days. The temperature is never less than 60° or more than 100° C. You might ask the same question that has so often been submitted to us in the form of a suggestion, as a measure of economy and convenience. "Why don't you sterilize all your ampoules in boiling water for 1 to 3 hours and accomplish the task rapidly, efficiently and economically?" As an answer to this question I will try to explain to you the necessity and what the advantages are of so-called fractional sterilization.

A great many of these delicately adjusted ampoule solutions cannot be subjected to the temperature of boiling water, for the length of time necessary to sterilize them, without partially, if not completely, decomposing the product. Consequently these solutions will no doubt be sterile, but they will have little or no therapeutic value.

The majority of bacteria with which ampoule solutions are liable to be contaminated, can be destroyed at the comparatively low temperature of 60° C. Many of these bacteria are spore-bearing, and while the bacteria can be destroyed at 60° C., the spores are resistant and can only be destroyed at the high temperature of 100° C.

A spore is a minute ovoid body in certain organisms, which gives rise to new organisms by germination. As for example, a solution may be contaminated with spore-bearing bacteria and sterilized at 60° C., on the 1st day the bacteria would be destroyed, but the spores will only be incubated and inside of 12 to 24 hours develop into bacteria; on sterilizing the 2nd day, this newly developed bacteria would be destroyed, and if any spores remained, that were not incubated during the first sterilization, which is very probable, they will be incubated during the second sterilization, and then develop into bacteria, which would be destroyed by sterilizing on the third day. After the ampoules have been sterilized, samples are sent to the Biological Department, where a bacteriologist tests them for sterility. It requires 5 days to complete this test.

To detect imperfect sealing, flaws in the glass, which up to this stage of the process did not appear, and cracks caused by being jostled about in the sterilizing boxes, we submit the ampoules to what we term a Blue Test.

Blue Test.—The blue test is made in the following manner: The metal box, containing the sterilized ampoules, is placed in a vacuum box that is partially filled with water in which is dissolved a small quantity of methylene blue. The cover of the vacuum box is clamped down and suction applied, which draws out the solution from the defective ampoules; then when the vacuum is broken by opening the air vent, the air, as it enters the chamber, forces the methylene blue solution into these defective ampoules.

Washing.—The ampoules are washed by immersing the box containing them first in warm soap suds, then clear water; those containing blue water are picked out and discarded, and the perfect ones are set aside to drain; they are then ready for finishing.

Finishing.—The special shaped ampoules are labeled and cartoned by hand; the others by machine. We have machines that label from 50 to 60 ampoules a minute, and carton them at the rate of 40 to 50 a minute. The ampoules are so packaged that they are always in an upright position, and the stems well protected, so that they will come into the consumers hands in a perfect condition.

In order to maintain aseptic conditions in the department where ampoules are manufactured, it is absolutely essential that everything must be kept scrupulously clean. All cleaning and dusting should be done at night or at a time when manufacturing is not in progress. All employees in the department are clothed in white uniforms, not for the sake of appearance, but to impress upon them the necessity of cleanliness.

LABORATORIES OF PARKE, DAVIS & CO.,
DETROIT, MICHIGAN.

IF THE DRUGGIST'S LANDLORD RAISED HIS RENT WOULD HE BE JUSTIFIED IN ACCUSING THE LANDLORD OF PROFITEERING?*

BY FRANKLIN M. APPLE

In these stirring, troublesome war-times one repeatedly hears of profiteering; also of increases in rent, and frequently the profiteering and rent-raising accusations are directly associated.

The latter cases are the ones we will take up briefly for consideration, and endeavor to ascertain if there is any justice in the charge that an increase in rent, at this time, by a landlord justifies the accusation that he is a profiteerer.

In order that we may reach a clear and just decision, it is absolutely necessary that we carefully analyze the question, and "lay upon the table," as it were, the facts in the case as they apply to both parties concerned.

What are the facts involved?

The landlord supplies the property, which represents an investment of his funds, from which he is entitled to a fair net return, as interest earned by said funds.

The druggist supplies the tenant, upon whom the landlord depends, for income from his investment in the property, for, if the property were unoccupied, it would prove to be a source of expense instead of a source of income to the landlord; hence it can be seen that each one is a benefit to the other one.

The question as to profiteering upon the part of the landlord, quite obviously, depends upon the amount of net income he demands from his funds involved.

I will call your attention to the fact that I lay stress upon the question of *net income* enjoyed by the landlord as a reward for the use of his funds, the care needed in overseeing the upkeep of the property and the risks assumed by him.

Let us consider some of the facts in the case that cannot be ignored.

When considering the question of upkeep of a property we are confronted by the cost of materials and the demands made by the artisans and the laborers for their skill and labor, and everyone who has had any experience along this line can vouch for the unprecedented advance in price of these essential factors. When

* Read before the Pennsylvania Pharmaceutical Association, 1918 meeting.