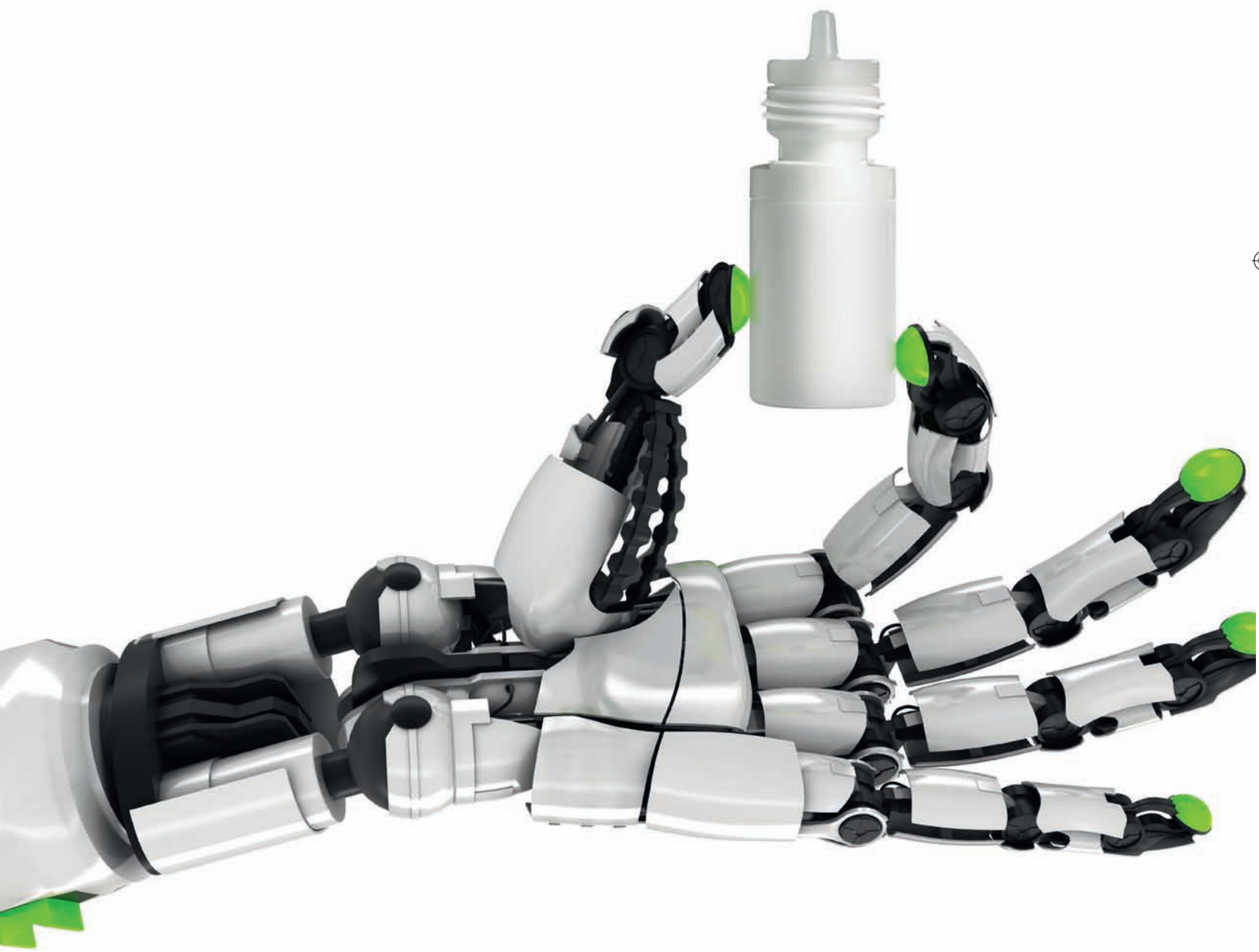
ABAK

Pure technology in a bottle



The history of a technological ⓡ -evolution

Théa
Driving innovation

Treat whilst preserving the integrity of the eye

The history of a technological (r)-evolution

The use of preservatives has enabled considerable advances to be made in the food-processing, cosmetics and pharmaceutical industry. The industrialisation of eye drops, which are more easily contaminated than ointments, has drastically changed.

My father, Jean Chibret, was the pioneer who introduced for the first time, a mercurial derivative then, a decade later, benzalkonium chloride, a more potent and less allergenic compound. Nevertheless, the repeated instillation of all these preservatives did not only give rise to expected effects, but over the years were also found to be harmful to the ocular surface.

The pharmaceutical industry therefore looked for new alternatives to eliminate the use of preservatives; single-doses for single use were one evidence of this, a multidose bottle without preservatives, much less so.

I am very happy that Laboratoires Théa were able to respond to this need after 10 years of research with the first preservative-free multidose bottle: the ABAK bottle. I chose this name as "A" signifies free from "BAK" or benzalkonium. Over 15 years, we have made numerous changes to the ABAK bottle with the aim of fully satisfying the expectations of prescribers and patients alike. Today, the ABAK bottle has become the most used preservative-free bottle in the world with several million units sold every year.

It is this pursuit that we are going to recount.

Henri CHIBRET - Chairman of Théa Holding

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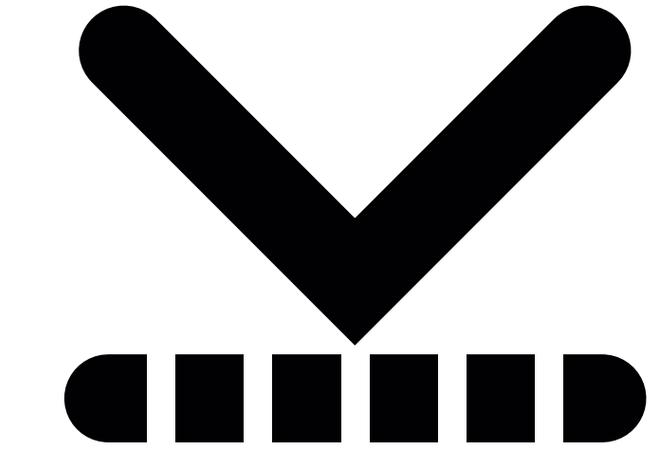


I. The history of ABAK

INTRODUCTION

When Henri Chibret asked me to reflect upon a preservative-free bottle, my initial idea was quite simply to place an antimicrobial filter at the end piece of the eye drops dropper. However, it was impossible to expel a single drop as the filtrating surface area was too small.

On the basis of this finding, the research and development team of Laboratoires Théa optimised this filtration system by enlarging it and by placing it directly within the bottle. We also made sure to avoid a permanent contact between the liquid and the filter so as not to damage it both during the period of storage and during use.

After having studied numerous avenues of research, undertaken tests, trials and experienced several failures, we found a technical solution to isolate the membrane of the solution: the ABAK bottle was thus born.

Though seemingly simple, this miniaturised bottle is in fact the concerted effort of research and technology, permitting the easy handling of the bottle by patients. Laboratoires Théa have been able to bring together a pool of high technology specialist companies in the fields of plastics technology, filtration, welding, microbiology and the physical chemistry of polymers etc.

Each detail of this bottle is not without its significance and justification. This explains moreover why more than 90 modifications have been necessary in order to perfect the ABAK bottle.

Michel FAURIE - Engineer

BOTTLES THROUGH THE AGES

The eye drop bottle prior to opening

At the start of the 20th century, when the pharmaceutical industry began to take an interest in the manufacture and packaging of ophthalmological products, ointments were preferred, being easier to manufacture and less contaminable.
The main problem for manufacturers was the production of solutions capable of remaining sterile over lengthy periods of time up to the opening of the container.

Up to the 1950s, this objective was attained using glass blown bottles, the watertight closure of which was undertaken manually in the presence of heat.
These containers were fragile, difficult to seal after opening and delicate to transport.
The emergence of heat-labile active substances – notably antibiotics – required the filling of bottles in a sterile room with a lyophilisation process frequently being required.
These procedures were facilitated thanks to "penicillin-type" moulded glass bottles closed by a notched rubber stopper. When necessary, a vial of solvent was added to the carton.
During use, the notched stopper was replaced by a plastic dropper. This type of packaging is still used.

However, given the persistent problem of the fragility of glass and its weight, manufacturers favoured plastic bottles (of the polyethylene type) from the time of their appearance on the market (1950), with however specific disadvantages such as the need to sterilise the bottle prior to filling (which required the use of ethylene oxide, a dangerous product to handle and costly installations), the plastic-eye drops interaction, the permeability of the walls to air, etc.

The appearance of a new packaging technology, the "blow-fill-seal system" then enabled in the 1970s, thanks to an extremely sophisticated material, to undertake the moulding and the filling of the bottle in a sterile environment in a single operation.

First preparations for
ophthalmological use

XVIth century

Flame-sealed,
blown glass bottles
and heat sterilisable

Onset of the XXth

Moulded glass bottles sealed
by a rubber stopper, maintained in
place by a crimped ring, and capped
by a plastic dropper end piece
at the time of use

1945

Polyethylene bottles
sterilised by ethylene oxide

1950

The eye drop bottle after opening

Though these successive technological advances resolved the production and packaging problems of a sterile product, the problem of contamination after opening of the bottle persisted. Laboratories Chibret had the first idea of systematically adding a preservative into the eye drops to fight against the proliferation of micro-organisms. This practice was rapidly adopted by all manufacturers.

The French and European Pharmacopoeia made the addition of preservatives compulsory for multidose eye drop bottles.
Mercurial derivatives such as Thiomersal were preferred.

This antimicrobial preservative, which was not harmful to the ocular surface, was found however to be highly allergenic, which quickly led manufacturers to investigate other preservative agents.

Preference was given to the quaternary ammoniums, such as benzalkonium chloride, a much less allergenic compound, with both potent antibacterial and antifungal properties. However, after some years of use, harmful effects were found on the ocular surface. Moreover, the presence of a preservative is not a guarantee of non-contamination of the content of the bottle as shown in numerous studies...
The emergence of the undesirable effects of these preservatives, which were toxic to the ocular surface, especially in the case of long term treatment, led manufacturers to show a preference for single-dose containers during the 1960s. These dispensers were originally developed in England at the request of the British Ministry of Health, following a major "epidemic" of endophthalmias in a Birmingham hospital. These endophthalmias were due to the use of contaminated products containing little or no preservatives.

Initially intended to limit nosocomial infections, the single-dose products are now used more and more due to the absence of preservatives.
These single-doses are mainly manufactured according to the "blow-fill-seal" principle and can contain less than 1 ml of solution each; their main disadvantage being the very high cost of manufacture and their difficult handling by the elderly or by those with handling difficulties.
The significant cost of manufacture of single-dose containers encouraged the research and development of multidose bottles capable of delivering several hundred drops without risk of microbial contamination of the container after opening (European Pharmacopoeia 01/2008: 1163).

But how can the sterility of the ophthalmic solution in the bottle during its use be guaranteed with a multidose bottle without preservatives? Laboratoires Théa were the first, following 10 years of research, to find an answer to this question, thanks to the development of the ABAK system which guarantees the sterility of the solution in the eye drops without the addition of a preservative. The very first ABAK system adsorbed the preservative when the eye drops were released at the time of instillation.

This in itself gave rise to successive technological developments ending in 2005 with the third generation of ABAK, currently marketed by Laboratoires Théa.

Single-doses

1960

ABAK 1st generation

1989

ABAK 2nd generation

1998

ABAK 3rd generation

2005

II. The ABAK system

A HIGH TECHNOLOGY BOTTLE

Nothing is simpler in appearance than an ABAK bottle ready for use, a slight pressure to the bottle and a single calibrated drop is produced.
But this simplicity conceals some mystery and calls for answers and explanations to questions which we are frequently asked:
"Why does this bottle retain the same size as a normal bottle?"

"Why is this bottle opened and handled like a normal bottle?"

"How can the tip permit the delivery of such a precise drop?"

"Why is the pressure applied to release a drop similar to that of a normal bottle?"

"How can the solution in the bottle remain sterile for 8 weeks?"

"How is it that the drops released are so strictly comparable?"

The ABAK system, made of a complex and high precision fitting of many parts, has been the subject of ten years of research, of development and of testing, so that each of its constituents might be adapted to its purpose: plastic materials optimised for each constituent, optimal deformability of the container, bacteriological filter, ideal shape and dimensions of the tip...

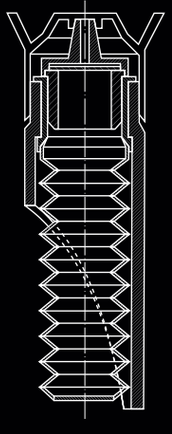
Each part of the device has been meticulously thought out and developed, giving rise to multiple invention patents, ending with a technological masterpiece, carefully placed within the ready for use bottle for an absolute simplicity of use.

But let's scrutinise a little the technology of the system...

Advances in the system

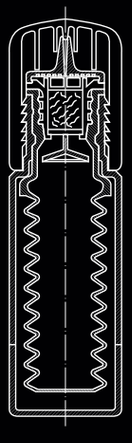
1989
ABAK 1st generation

1998
ABAK 2nd generation



PATENT N°1 + N°2

Elastically deformable recipient
= re-aspiration of the liquid without aspiration of air



PATENT N°3

Neutral microporous pad
+ preservative-free solution

2005

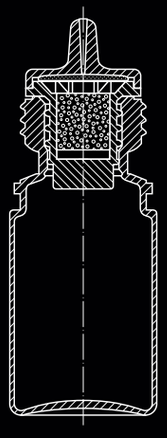
ABAK 3rd generation

105 mm

102 mm

70 mm

SCALE 1:1



PATENT N°5

Bi-functional membrane
+ preservative-free solution

ABAK today

Reservoir containing up to 300 sterile drops
(10 ml bottle)

Flexible and ergonomic wall
made of low density additive-free polyethylene

Locking system
thanks to anti-violability ring

Neutral microporous pad

Bifunctional PES membrane
hydrophilic / hydrophobic 0.2 µm

Rounded protective tip

Calibrated preservative-free
drops (30 µl)

The ABAK bottle permits up to 8 weeks of treatment after opening

AN INNOVATIVE CONCEPT

a. Membrane and evolutions

The first patented ABAK system undertook the purification of the solution by adsorption of the preservative onto a porous pad at the time of delivery of each drop. Though ingenious, this system had a major development limitation: the porous pad could also partially adsorb certain active ingredients, such as timolol. All formulations could not therefore benefit from the ABAK system.

A decisive development, consisting of removing the preservative from the formulation, enabled the ABAK system to be extended to almost all solutions for which the viscosity was compatible with the use of an antimicrobial membrane with a 0.2 µm porosity which protects the eye drops from contamination by micro-organisms the size of which vary from 1 to 10 microns. In the first generations of ABAK bottles, the hydrophilic antimicrobial membrane not being permeable to gases after moistening, the release of drops was not compensated by an intake of air. This therefore created a vacuum requiring recourse to a deformable reservoir.

This, in the shape of an accordion, was itself enveloped by a rigid external shell. This unusual concept, which sometimes gave rise to visible deformations and a poor return to shape of the flexible bottle, was a concern to users. Handling was also changed at the end of treatment when the pressure required for the expulsion of drops became greater and greater as the quantity of eye drops in the bottle diminished.

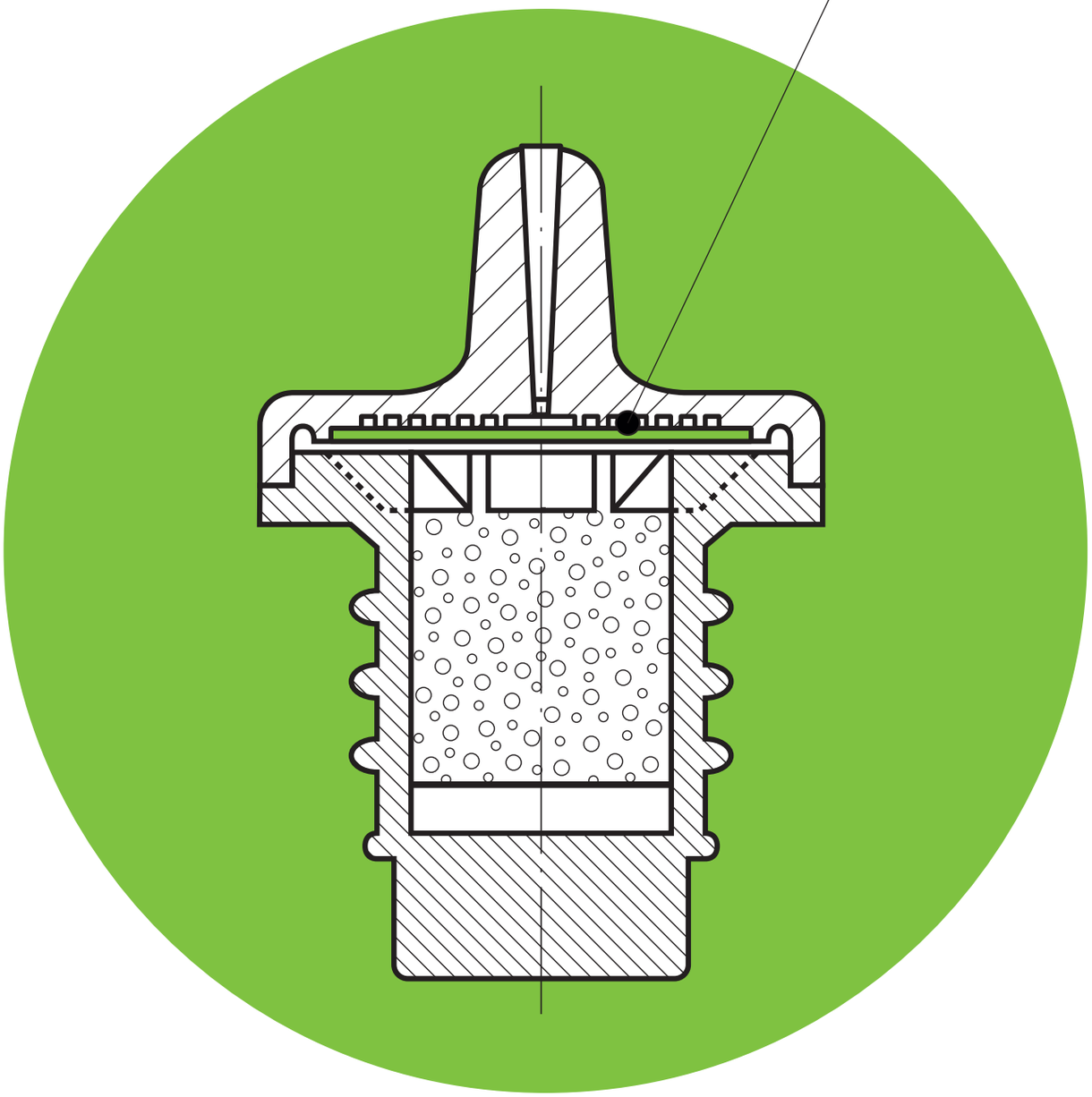
A genuine technological leap took place with the arrival of a new membrane, which was both hydrophilic and hydrophobic, which would enable start-up implementation by the patient to be avoided and would give the ABAK bottle the size and shape of a traditional bottle.

This hydrophilic polymer membrane is rendered in part hydrophobic by a patented surface treatment. Developed by PALL Ltd, a world leader in filtration and under the impetus of Laboratoires Théa, this revolutionary membrane made from a P.E.S* based compound, required years of development: it was found to be capable of accepting a surface treatment defining a hydrophobic zone to be joined to a different material consisting of the tip, then of being sterilised. None of these well validated processes altered its antimicrobial barrier properties.

*P.E.S: polyether sulfone

REVOLUTIONARY MEMBRANE

P.E.S* based compound

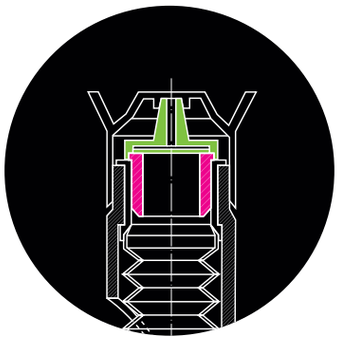


In order to prevent the antimicrobial membrane from being in permanent contact with the solution during the period of storage prior to use, various systems were used with the disadvantage of requiring the patient to screw or unscrew the stopper which capped the bottle. These disadvantages were eliminated in the 3rd generation by the combined action of a hydrophobic porous material placed in the head of the bottle and by a stopper closing the end of the tip in a watertight manner. This original device, having been patented, also allowed the flow of liquid leaving and the air entering to be regulated.
The ABAK bottle thus enables a true drop-by-drop administration, the patient being able to instil one drop after another, thus avoiding waste.

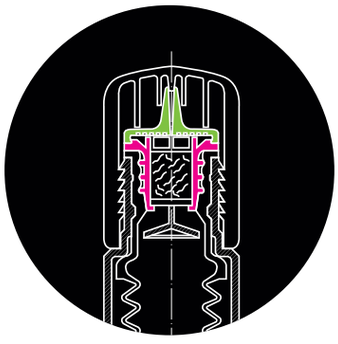
b. Plastic and pressure

Membrane, foam pad and dropper favour a controlled flow of drops and prevent the output of eye drops in beads or in run-offs. The deformability of the body of the bottle under pressure on the other hand, plays a key role in facilitating the output of drops.
The choice of plastic material from which the body of the bottle is made turns out to be determinant, likewise the thickness of the wall. A compromise was reached between a sufficient thickness to limit permeability and a flexibility permitting the deformability of the bottle with a minimal pressure so as to facilitate the ejection of drops by the patient, even the elderly or those handicapped by arthritis.

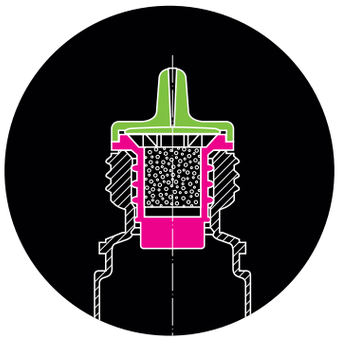
PATENT N°1 + 2



PATENT N°3



PATENT N°5



c. The tip and the drop

Each solution forms drops with different superficial surface tensions, viscosities and densities. It is therefore seemingly impossible to obtain a calibration of the size of drops ensuring that each bottle supplies, in theory, 300 drops per 10 ml bottle, irrespective of the density and the viscosity of this solution. Ideally, the tip should be adapted for each eye drops, but this not being possible from the manufacturing standpoint, the flow has been calculated from mean data so as to be suitable for all eye drops.
With remarkable precision, given that the French Pharmacopoeia XXth edition of 1990 tolerates variations of 30%, the variability interval of the size of the drops produced by the ABAK system (approximately 30 microlitres) is much lower than this threshold.

Such a result has been obtained on the one hand by the regulation of flow linked to the foam pad and to the filtrating membrane, but also, thanks to the meticulous adjustment of the diameter and of the shape (opening out from the base) of the dropper channel, forming customized drops.

Furthermore, a distinctive "ring" shape has been moulded at the extremity of the dropper, so as to permit the detachment of each drop for a given threshold of surface tension. It is thanks to this characteristic that the size of the drops is calibrated and that each 10 ml bottle can thus deliver precisely 300 drops.

A BOTTLE OF HIGH SECURITY

In the early generations, the inviolability of the ABAK bottle was provided by an outer film of heat-shrinkable cellophane all around the bottle that the user had to remove before use.

This device, very common in pharmaceutical and cosmetic industries, accounted for an additional industrial operation and an additional difficulty for users, especially for visually impaired or unskilled seniors.

Indeed, this transparent film is virtually invisible. The outer film has been replaced by an anti-violability ring that can be easily broken. Proof of first use is provided when this seal is broken.

AN ORIGINAL CONCEPT UNDERGOING CONTINUOUS EVOLUTION

a. Contribution to quality

A quality policy with the aim of zero defects and 100% satisfaction calls for complete processing of all observations.
To achieve this, since it was first introduced on the market, the development of the ABAK system has mainly taken as its source the increase in observations from patients and ophthalmologists. Preoccupations concerning bottle shape changes, excessive pressure needed in patients with arthritis of the hands...

Each improvement has had the aim of producing a simpler and more efficient bottle in its use in order to improve the degree of satisfaction of patients and prescribers.
It should be noted that ABAK has been the subject of numerous monitoring tests, and in particular, all the tip membranes are verified.

b. What is the future for ABAK?

Are further improvements possible? The ABAK bottle satisfies the user both because of its size and its handling capability.
Nevertheless, it is unsuitable for viscous solutions, gels and for liquid gels for which the only alternative in the absence of a preservative is a single-dose system.
Laboratoires Théa are undertaking research studies to resolve this problem.

PATIENT SATISFACTION

/ MAINS SURVEY /

The difficulty of instilling eye drops is a poor compliance factor limiting the therapeutic efficacy of treatment. A large number of studies suggest a cause and effect relationship between the instillation technique of the drops or the difficulty of using the product and the poor compliance of patients [1-7].
Patients often frequently experience difficulty in ejecting the drops, opening the eye drops bottle or in holding it [2,4].
To our knowledge, there is little comparative published data on the ease of use of various methods of administration and on patient preference vis-à-vis these different systems.
Acknowledging this, Laboratoires Théa undertook a survey called MAINS [8] (Manipulation, Acceptability and Instillation of a New bottle without preservative) in order to better appreciate the problems encountered by patients during the use of eye drops.
The aim of this study was to more specifically evaluate the handling capability and overall acceptability of a timolol based eye drops in an ABAK bottle compared to other methods of administration (preserved multidose eye drops with preservatives or single-dose) in patients treated for glaucoma or ocular hypertonia.
This retrospective, multicentric and transversal study involved 41 ophthalmologists throughout France with the aid of 654 patients with an average age of 66 years.

All patients received a complete or partial substitution of their treatment; a beta-blocker packaged in an ABAK bottle (FIG.1) and answered a questionnaire after duration of use of at least 1 month.
In the MAINS survey, patients were virtually unanimous regarding the handling capability of the ABAK bottle:
- **easy opening reported by 96.5% of patients,**
- **easy handling by 96.0%,**
- **easy drop dispensing by 91.1%.**

Out of all these criteria and overall, patients preferred the ABAK bottle compared to the preceding packaging. These results were confirmed in the most elderly patients, i.e., those who encountered the greatest difficulty in instilling their eye drops.
It is important to stress that the handling capability and acceptability of the ABAK bottle was deemed to be even more favourable in patients previously using the single-doses.

Thus,
- **25% of patients previously treated with single-doses and unable to treat themselves without help, were able to instil their treatment themselves thanks to the ABAK bottle;**
- **overall more than 76% of patients treated with single-doses preferred the ABAK bottle to their preceding eye drops.**

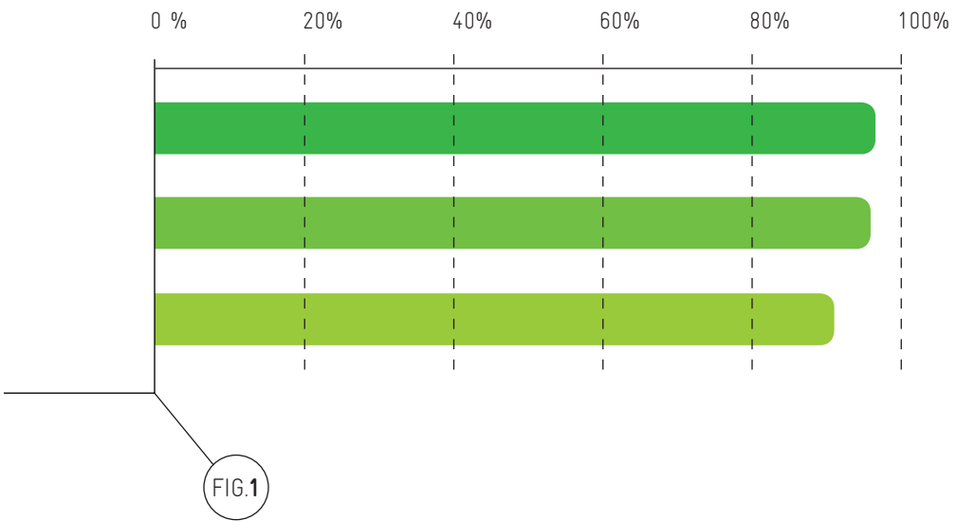


FIG.**1**

Glaucoma and more generally the increase of intraocular pressure are chronic and progressive pathologies. Often, for the patient, the problem is not the disease itself but its treatment. Insufficient compliance leads to bad control of the intraocular pressure.

Particular age-related conditions (decrease of visual acuity, neuromuscular problems...) can have an impact on the eye drops use.

In particular, a study has shown that age (≥ 60 years old) was associated with inappropriate instillation of drops [1]. A study performed in ≥ 75 year-old eye drop users shows that 50% of them have some difficulties in instilling the drops [6]. Another study shows that 17% of glaucomatous patients have to be assisted for the instillation [4].

A significant proportion of patients would need some help for the instillation of drops [2, 4].

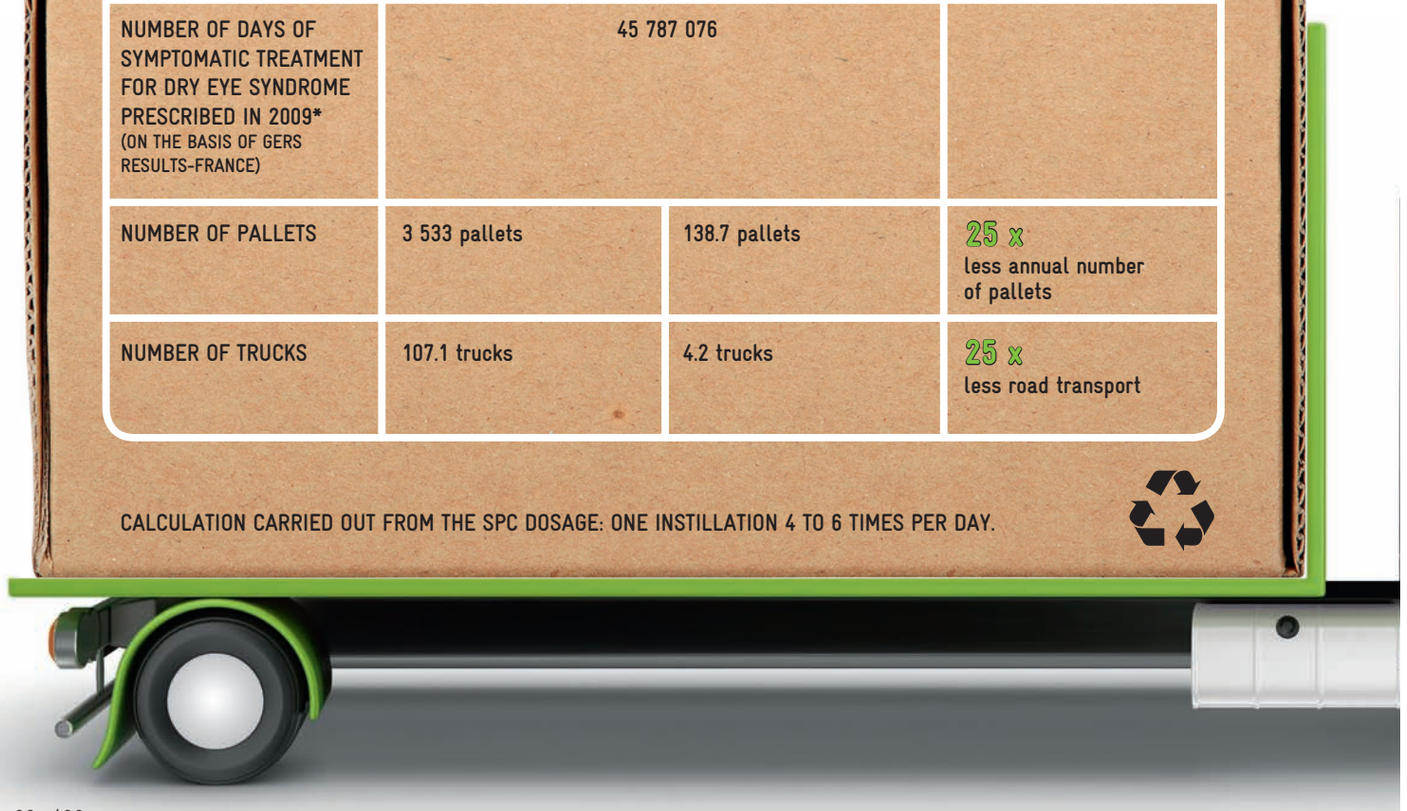
The results of this survey have shown a good handling and acceptation of ABAK bottle:

• 98% of patients followed their treatment correctly,
• 96% of patients instilled their treatment themselves,
• 96% of patients considered it to have an easy opening,
• 91% of patients appreciated the easy instillation of drops,
• 96% of patients considered it to have an easy handling,
• 29% of ≥ 60 year-old who needed some help to instil the eye drops, could instil their treatment themselves.

Consequently, the ABAK system could be privileged in recurrent and chronic ocular pathologies such as glaucoma, dry eye or allergy.

	LACHRYMAL SUBSTITUTE IN BOXES OF 36 SINGLE-DOSES	LACHRYMAL SUBSTITUTE IN ABAK BOTTLE	BENEFIT
SIZE OF SECONDARY PACKAGING	0.411 dm^3 (189 x 75 x 29)	0.124 dm^3 (96 x 36 x 36)	Linear area **3 %**
SINGLE CARTON VOLUME	0.0185 m^3 (45 boxes / carton)	0.0186 m^3 (150 boxes / carton)	
VOLUME OF A PALLET	1.29 m^3 48 cartons / pallet (120 x 80 x 134)	1.39 m^3 44 cartons / pallet (120 x 80 x 145)	
LOGISTICS / TRANSPORT (THEA)	33 pallets / truck		
1 PALLET REPRESENTS:	12 960 days of treatment	330 000 days of treatment	**x 25** number of treatments per pallet
NUMBER OF DAYS OF SYMPTOMATIC TREATMENT FOR DRY EYE SYNDROME PRESCRIBED IN 2009* (ON THE BASIS OF GERS RESULTS-FRANCE)	45 787 076		
NUMBER OF PALLETS	3 533 pallets	138.7 pallets	**25 x** less annual number of pallets
NUMBER OF TRUCKS	107.1 trucks	4.2 trucks	**25 x** less road transport

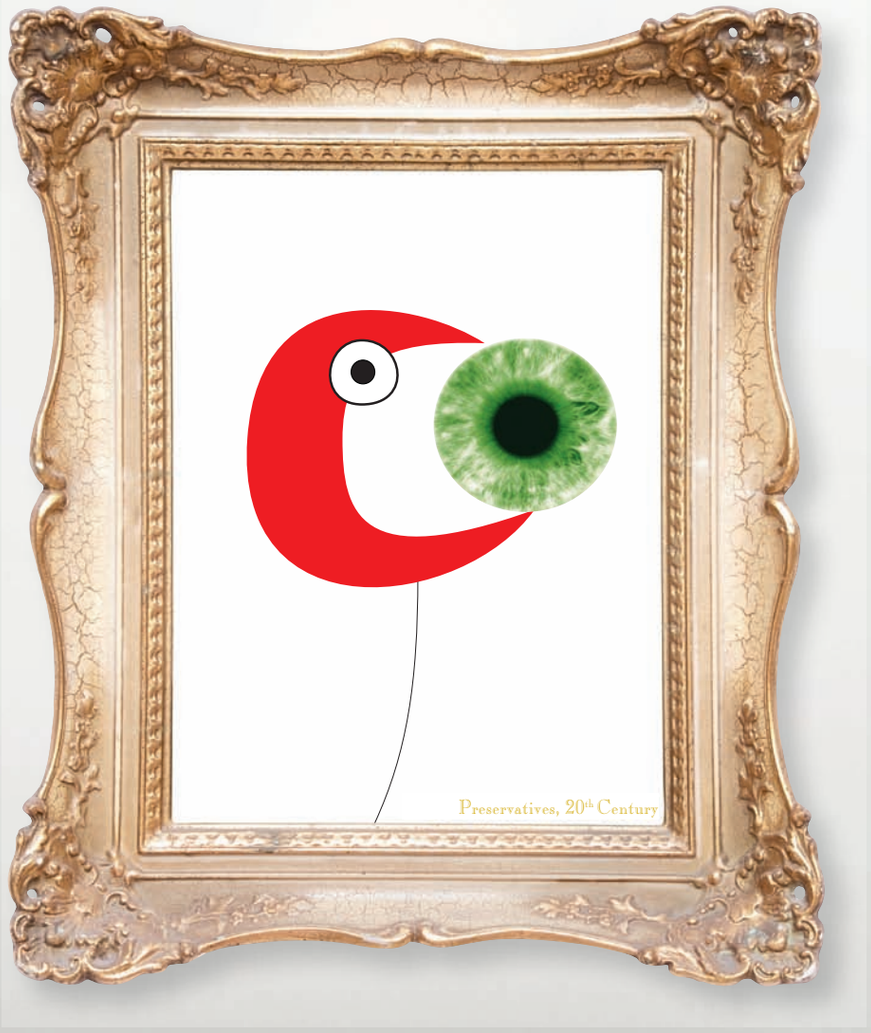
CALCULATION CARRIED OUT FROM THE SPC DOSAGE: ONE INSTILLATION 4 TO 6 TIMES PER DAY.



INNOVATION FOR THE BENEFIT OF ECOLOGY AND THE ECONOMY

As a general rule, all disposable products in the field of healthcare as in other fields include a high ecological cost.
In ophthalmology, the multidose bottles are widely preferred as they generate a lot less waste.
A 10 ml ABAK bottle contains 300 drops, or 150 instillations for 2 eyes, or the equivalent of 150 single-doses.
The table illustrates the ecological benefit of an annual artificial tear treatment in an ABAK bottle compared to its equivalent treatment in single-doses: if all the lachrymal substitutes were prescribed using ABAK, there would be 25 times less road transports than with an exclusively single-dose market.

ABAK is an "ECO-EYE DROPS" both ecological and economic.



III. History of preservatives

Preservatives and their harmful effects in ophthalmology

GENERAL POINTS

Preservatives are used in the pharmacopoeia in order to preserve the sterility of medicinal solutions and eye drops in particular during their duration of use which is limited to 15 or 30 days after opening.
However, the presence of a preservative is not a guarantee of non-contamination of the bottle contents as shown by numerous studies.

There are various classes of preservative, the common characteristic of which is antimicrobial activity, mainly antibacterial and in addition, antifungal in some cases.
The most commonly used preservatives in ophthalmology are the quaternary ammoniums, notably benzalkonium chloride or cetrimide. The quaternary ammoniums are highly hydrophobic bipolar antiseptics, having surfactant and detergent properties thanks to which they are capable of emulsifying lipids and dissolving lipid membranes.

The other class includes mercurial derivatives which act by binding with sulphydril groups of proteins from living organisms leading to their precipitation. They are no longer used due to their high allergenic potential and mercury toxicity.
The amidines, mainly represented by chlorhexidine, act by destroying the semi-permeable layer of cytoplasmic membranes.
Oxidising complexes known as "soft preservatives" such as sodium perborate or chlorite derivatives, produce oxidising derivatives denaturing lipids, proteins or DNA. The chlorites in particular, give rise to a marked oxidation of glutathion, thus further reducing the anti-oxidising defences of cells.

The principal problem posed by preservatives that can already be discerned from this brief description, resides in the essence of their mechanism of antimicrobial action and consists of a non-specific biological activity the aim of which is to destroy living cells by membranous solubilization, an increase in ionic permeability and/or an inhibition of cellular metabolism.

Though this toxicity is fortunately more marked in micro-organisms, it is not without an effect on eucaryotic cells, in particular the very fragile and very exposed cells of the cornea and conjunctiva.

Though generally without major consequences during short term treatment, the opposite is true during long term use. In fact, the preservatives are potentially toxic to all the structures of the eye, not only on the surface (conjunctiva, cornea) but also deep seated ones (trabeculum, lens and retina).

TOXICITY OR ALLERGY?

Preservatives are very occasionally responsible for a contact allergy. However, sensitisation to preservatives should have a tendency to increase given their presence not only in eye drops and contact lens cleaning agents, but also in many products in current use (soaps, cosmetics, disinfectants...) [9].

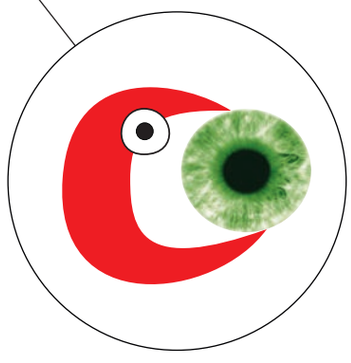
The mercurial derivatives are highly allergenic (13 to 37% depending on the series) [10, 11, 12] and benzalkonium salts are moderately allergenic (4 to 11% depending on the series) [10, 13]. Sensitisation to other preservatives is rarer. The reactions observed are most often contact allergies corresponding to type IV delayed hypersensitivity reactions which may be shown objectively by skin patch tests [14, 15].

From a clinical point of view, they are generally manifested by a picture of conjunctivitis, extending from a simple conjunctival hyperaemia to papillary conjunctivitis with or without eyelid eczema.

Though these latter signs may be fairly suggestive, in their absence, an allergic reaction to preservatives is often wrongly called to mind in the presence of cytotoxic phenomena, which are by far a lot more commonplace.

TOXIC EFFECTS ON THE OCULAR SURFACE

The cytotoxicity of preservatives mainly affects cellular viability through a change in the integrity of the plasma membrane or mitochondrial energy metabolism [16, 17, 18, 19], proliferation [20, 21, 22] or cellular adhesion [23]. Some cellular changes are irreversible and the removal of the preservative is not always sufficient for cellular restoration [24, 25, 26]. These cytotoxic effects are observed at concentrations lower than those usually used in eye drops and increase with the duration of exposure.



a. Detergent effect

Preservatives reduce the stability of the lachrymal film due to their detergent effect on the lipid phase, by a reduction in the number of mucus cells and by a change in transmembranous mucins. This detergent effect gives rise to an increased evaporation of tears and to ocular dryness, which can potentiate a possible pre-existing syndrome [27, 28].

b. Oxidative stress / Necrosis / Apoptosis

Benzalkonium chloride gives rise to a moderate activation of complement [29]. A release of toxic free radicals appears at extremely low concentrations (0.00001%). Cellular growth is halted at low concentrations (0.001%) [27]. At usual concentrations (0.005% to 0.01%), the quaternary ammoniums give rise to irreversible cellular changes and signs of apoptosis within 15 minutes. At higher doses (0.05 to 0.1%), a clear cut cellular necrosis is seen at the ocular surface [30, 31, 32, 33].

c. Inflammation

In patients treated long term with preserved anti-glaucoma eye drops, an infiltration of the conjunctiva by macrophages and lymphocytes is observed, the density of which is multiplied by a factor of 3 to 4. The inflammatory reaction is shown by the expression of HLA-DR leucocytic antigens and the adhesion molecule ICAM-1, which is essential for the cellular immunity reaction [29, 34]. Furthermore, an overexpression of certain receptors to chemokinins is seen in these patients, suggesting that the long term use of anti-glaucomatous eye drops with preservatives gives rise to a complex chain of inflammatory reactions [28].

The inflammatory reaction at the conjunctival level is responsible for changes in the conjunctival epithelium – loss of tissue cohesion [35], morphological changes affecting the epithelial cells, keratinisation and loss of mucus cells, apoptosis and a subepithelial fibrosis. All these abnormalities are absent in glaucoma patients treated in the absence of preservatives [27, 29, 36, 37]. Even in the absence of clinical manifestations, a number of publications have reported an abnormal inflammation of the conjunctival epithelium the intensity of which appears to be correlated to the number of eye drops instilled and to the duration of treatment [28].

The repeated application of benzalkonium chloride can also delay, even inhibit, cellular regeneration and repair of the rupture of the epithelial barrier [38, 39].
Finally, in the case of the prolonged administration of preserved eye drops, a chronic fibrosis develops which is a contraindication factor in filtration surgery: it has in fact been reported that the combination of several anti-glaucoma treatments multiplies the risk of failure by a factor of 5.

The overall lesional potential of marketed lachrymal substitutes containing different preservatives has recently been evaluated in an in vitro corneal epithelium culture model in acute and chronic administration (incubation of 24, 48 or 72 hrs) [40]. The results of this study suggest an overall toxicity for the majority of preservatives with a reduction in cellular viability, an increased production of interleukin 8 (IL8), histological changes to the epithelium with lesional phenomena and tissue necrosis. The expression of occludin, a tight junction transmembranous protein the over expression of which is an early marker of tissue lesions, is increased early on with all the preservatives and with a diffusion into all the layers of the epithelium.
However, one notable finding is that all the products free from preservative tested in this study did not give rise to such changes.

PRODUCT TESTED	TISSUE VIABILITY	HISTOLOGICAL ANALYSIS
Nacl 0.9% negative control	100%	Normal
BAK 0.1% positive control (toxicity +++)	0%	Tissue necrosis at all time measurement points
BAK 0.01% 24 hrs 24 + 24 hrs 72 hrs	(NS) 43% 0%	Early signs of toxicity Superficial lesions Tissue necrosis
Hydroxylpropyl methyl cellulose perborate 24 hrs 24 + 24 hrs 72 hrs	(NS) (NS) 75%	Early signs of toxicity Superficial lesions Deep seated lesions
Polyquad® **Hydroxylpropyl guar** 24 hrs 24 + 24 hrs 72 hrs	(NS) (NS) 70%	Early signs of toxicity Superficial lesions Deep seated lesions
Oxyd® **Sodium hyaluronate** 24 hrs 24 + 24 hrs 72 hrs	(NS) 71% 4.5%	Early signs of toxicity Necrosis Necrosis
Thiomersal **Sodium hyaluronate** 24 hrs 24 + 24 hrs 72 hrs	(NS) (NS) 1%	Necrosis at all measurement time points
Comod® **Sodium hyaluronate**	(NS)	Normal
Abak® **Sodium hyaluronate**	(NS)	Normal

REF 40
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Occludin gene expression as an early in vitro sign for mild eye irritation assessment.
Toxicol In Vitro 2010; 24 (1): 276-85.

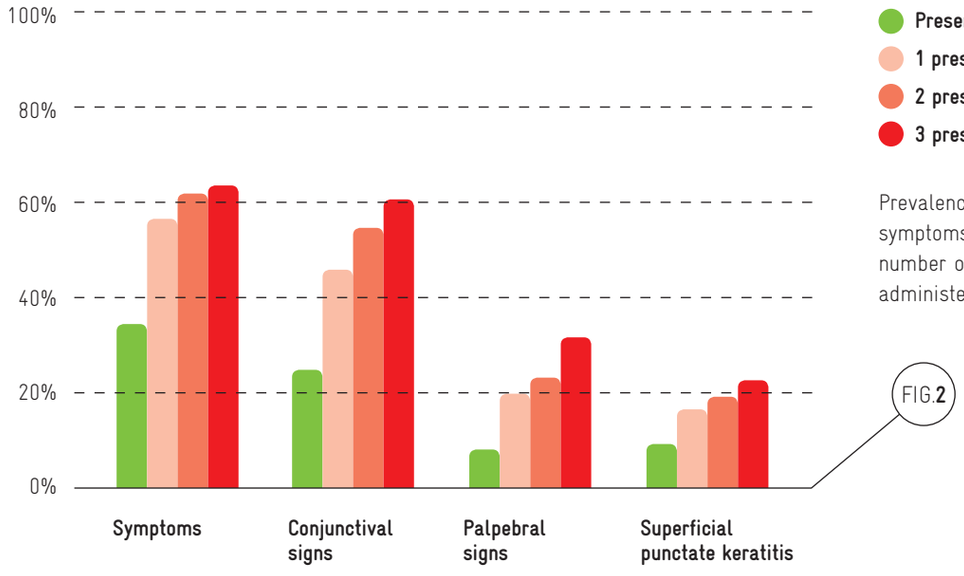
	IL-8	EXPRESSION OF OCCLUDIN	LOCALISATION OF OCCLUDIN
	Minimal	Normal	Normal: mainly fixed within the superficial layers
	Slight (due to severe toxicity)	Regulation + at 24 hrs Regulation – at 48 & 72 hrs	Disappearance of occludin in almost all layers of the epithelium
	↗ ↗ ↗ ↗	Regulation + Regulation + Regulation –	Diffuse fixation in the basal layers and disappearance in the most superficial layers
	↗ ↗ ↗ ↗	Regulation + Regulation + Regulation +	Diffuse fixation in the superficial layers
	↗ ↗ ↗ ↗	Regulation + Regulation + Regulation +	Fixation mainly in the superficial layers
	↗ ↗ ↗ ↗	Regulation + Regulation + Regulation -	Damaged, thinned epithelium with an abnormal distribution of occludin and poor labelling
	↗ ↗ ↗ ↗	Regulation + Regulation + Regulation -	Fixation mainly in the superficial layers
	negative id control	Regulation – (72 hrs)	Fixation mainly in the superficial layers
	negative id control	No change	Fixation mainly in the superficial layers

Thus, in the region of the superficial ocular tissues, at concentrations equal or less than those used in eye drops, preservatives induced changes in the lachrymal film and potentially severe lesions of the corneo-conjunctival epithelium extending from the more or less pronounced loss of microvilli [41] to a superficial necrosis and a loss of cohesion of the epithelial barrier.

The administration of several eye drops in combination can give rise to very high doses of benzalkonium chloride in the same patient with a risk of damage to the ocular surface doubling with each daily supplementary drop of eye drops containing a preservative [42]. A study carried out in 2004 in glaucomatous patients thus found lesions of the cornea and conjunctiva of a severity proportional to the concentration of benzalkonium chloride in the eye drops [43].

TOXIC EFFECTS ON INTERNAL OCULAR STRUCTURES

The conjunctival and corneal epithelium behaves like a true reservoir: very quickly saturated, it can progressively release the preservative and redistribute it in the lachrymal film or in other ocular tissues. Animal studies show that benzalkonium chloride accumulates in the corneo-conjunctival epithelium and in the stroma and that it is also detected in deeper structures: lens, iris, vitreous body, choroid and retina [43, 44]. Its degradation is slow and its half-life is long.
In deep tissues, preservatives appear to be capable of inhibiting the growth of human trabecular cells even at low concentrations, a phenomenon which may be linked to changes in the trabeculum seen in glaucomatous patients treated over a number of years [45, 46]. The inflammatory phenomena associated with preservatives may explain the increased incidence of cystoid macular oedema after cataract surgery in patients treated long term with eye drops containing a preservative [47].
Finally, preserved eye drops can give rise to retinal lesions as demonstrated by the electroretinogram after only 15 days administration in animals [48], followed by a detachment of the retina, a loss of visual acuity and atrophy of the pigmented epithelium and of the choroid. These effects were not seen with preservative-free eye drops.

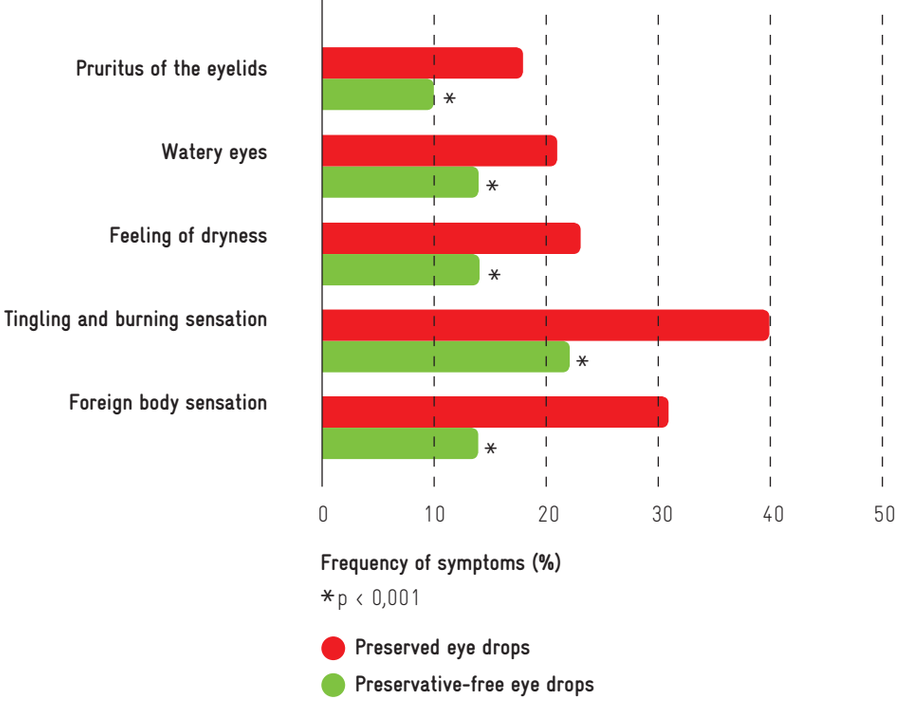


Prevalence of signs and symptoms according to the number of preserved eye drops administered to patients [51]

FIG.**2**

FIG.**3**

Frequency of symptoms reported by glaucomatous patients treated with preserved or preservative-free eye drops [50]



PRESERVATIVES AND TOLERANCE

Several transversal epidemiological surveys undertaken by ophthalmological practitioners have enabled the demonstration of the high prevalence of ocular changes in patients treated by preserved eye drops [49, 50, 51, 52].

A survey undertaken by 249 French ophthalmologists involving 1.181 patients and then repeated by 125 ophthalmologists on 850 patients treated with anti-glaucomatous eye drops found in 40 to 54% of cases that instillation was accompanied by discomfort or pain and that 51% to 58% of patients reported the presence of at least one symptom apart from during instillation [50, 52].

So during anti-glaucomatous treatment with an eye drops containing a preservative, the symptoms of a local intolerance, reported by patients as well as the signs observed by ophthalmologists, are at least 2 to 3 times more frequent than during treatment without preservative. The feeling of sand in the eyes (x 2.2), a stinging or burning sensation (x 1.8), ocular dryness (x 1.6), watering of the eyes (x 1.5) or itching (x 1.9) are significantly more common with preservatives (FIG.2).

It is also observed that the frequency of signs and symptoms increases with the number of preserved eye drops (FIG.3).

A transversal study [42] undertaken in 101 patients treated with antiglaucomatous eye drops found that more than half of the patients suffered from changes to the ocular surface: 59% of them had symptoms of ocular dryness in at least one eye, which was severe in 27%. The Schirmer test suggested a defective lachrymal production in 61% of patients and severe in more than half of the cases. A sub-study of the Woman Health Study and of the Physicians Health Study found that ocular dryness gives rise to a measurable change in the quality of life [53] and, in 2004, an association was reported between a loss of quality of life due to being partially sighted and the presence of local undesirable effects leading to dissatisfaction and poor compliance [54].

Compliance is a key issue in chronic disease such as glaucoma [55], which is insidious and asymptomatic, but which nevertheless requires life-long treatment. A treatment regarded by the patient as inconvenient, either due to numerous daily instillations [56, 57] or giving rise to undesirable effects [58], will inevitably be accompanied by a mediocre compliance thus limiting therapeutic efficacy. Indeed, a quarter of patients admit to having unpleasant secondary effects linked to their treatment [59] and these embarrassing secondary effects represent 64% of causes of non-compliance in glaucoma.

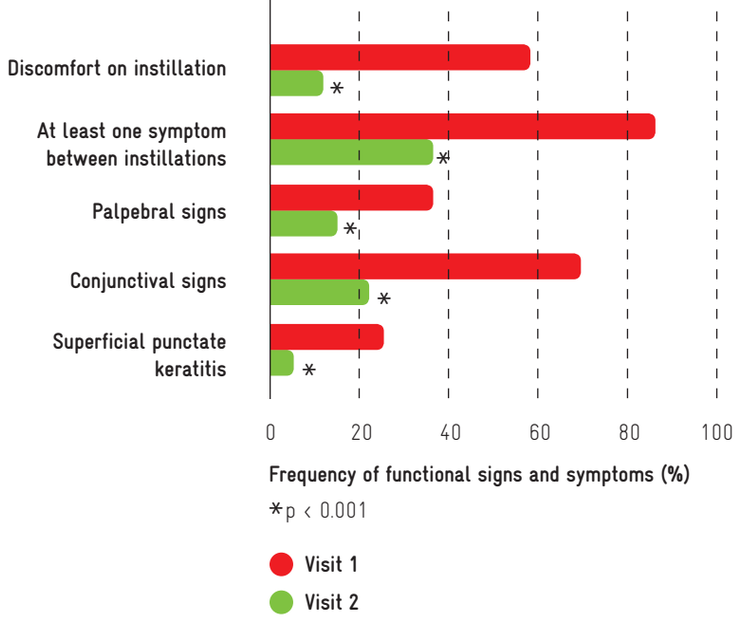
Finally, the withdrawal of eye drops with preservatives or their substitution with preservative-free eye drops gave rise to a highly significant improvement in these signs and symptoms (FIG.4). This has been confirmed by a large study carried out in 4 European countries on 9.658 patients treated with a beta blocker eye drops with or without preservative. Symptoms experienced by the patients as well as objective signs were all less frequent with the preservative-free eye drops ($p < 0.0001$):

- discomfort on instillation (19% vs 48%)
- sensation of a foreign body (15% vs 42%)
- stinging or burning (20% vs 48%)
- sensation of ocular dryness (16% vs 35%).

A significant reduction ($p < 0.0001$) in all the ocular symptoms and signs was observed in patients in whom treatments with preservatives were reduced or replaced by a preservative-free eye drops (FIG.5).

FIG.4

Frequency of functional signs and symptoms at inclusion (visit 1) and at 3 months after switching to preservative-free eye drops (visit 2) in glaucomatous patients [50]



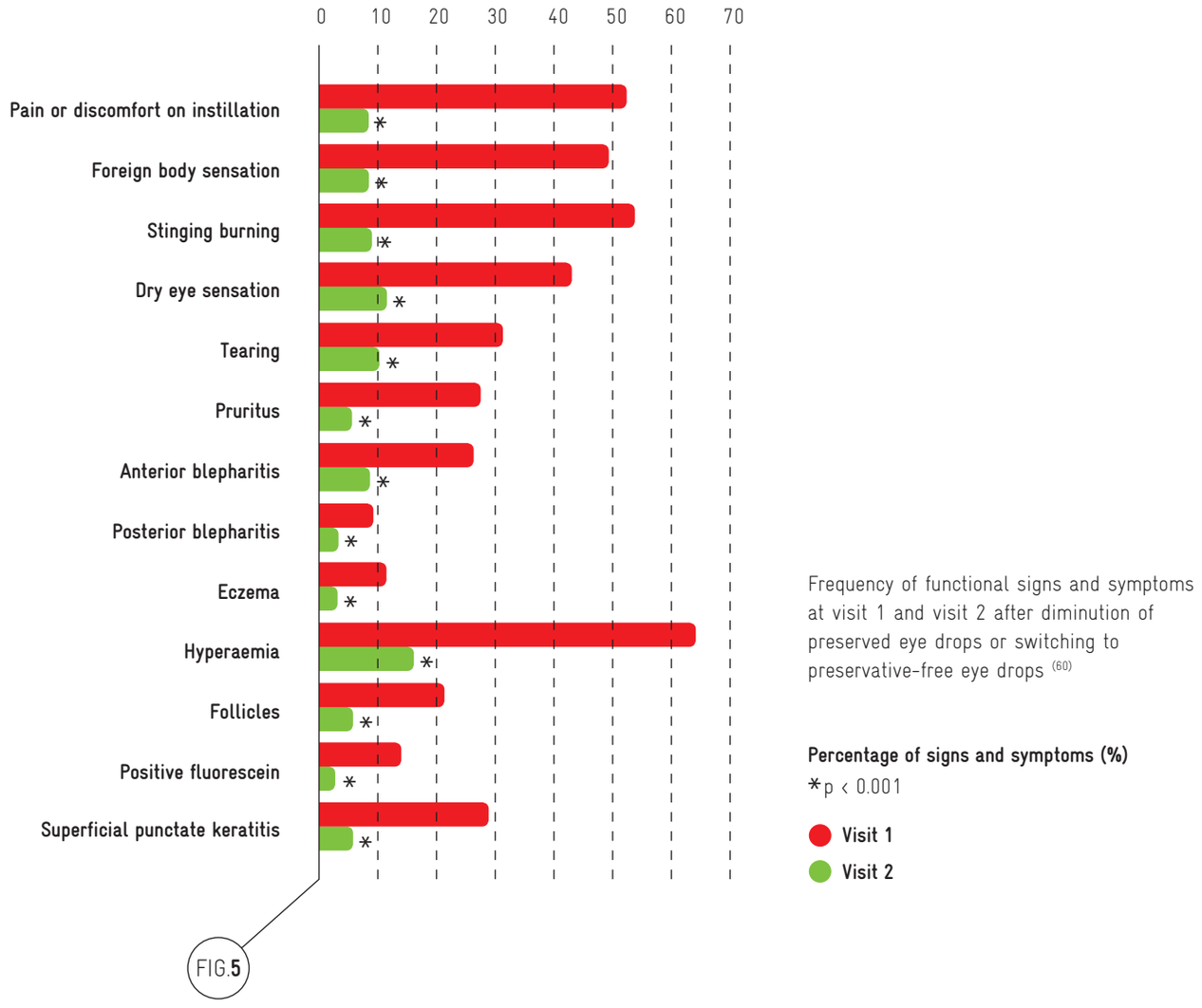


FIG.**5**

Several randomised clinical trials have assessed, for a short-term use, the tolerance of eye drops with and without preservatives: artificial tears [61, 62], local anaesthetics [63] and beta-blockers [64, 65, 66].
All of them have shown that preservative-free eye drops are better tolerated, are better accepted and respect the lachrymal film and corneal permeability.
Randomised studies performed for several weeks with cicatrizants [67], NSAID's [68], beta-blockers [69] and artificial tears [70, 71, 72] have also demonstrated the superiority of preservative-free eye drops in terms of ocular surface respect.

It is an obvious fact that preservatives are responsible for the symptomatic ocular surface alterations and can affect the quality of life, and the compliance and adherence to chronic treatments. The use of preservative-free treatment, if possible, should be privileged.

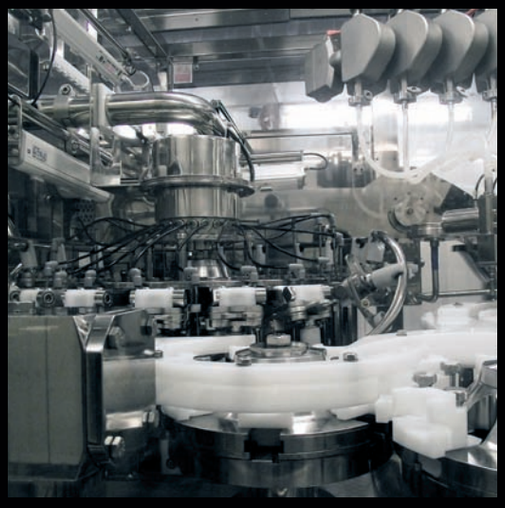
IV. ABAK worldwide

1 ABAK PRESCRIBED EVERY 3 SECONDS

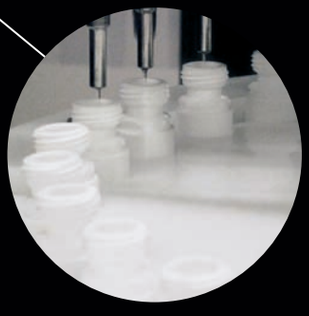
When I returned to Laboratoires Théa in 2001, the ABAK was already marketed in many countries. Its development was helped by the creation of 11 subsidiaries in Europe and by an important number of distributors around the world.
Today, we are present in 48 countries.
The success of ABAK is also due to the awareness of the harmful effects of preservatives on the ocular surface and in turn, due to the large number of preclinical and clinical studies undertaken worldwide.
Today there is a worldwide consensus on the benefit of avoiding the presence of preservatives in ophthalmic solutions.
ABAK has therefore opened up the "preservative-free" route which, little by little is spreading throughout the world.

Jean-Frédéric Chibret - President of Laboratoires Théa

14 brands
in 8 different therapeutical areas
are marketed in 48 countries



Production site of ABAK – Laboratoires Théa – Milan



PRODUCTION

Whilst Laboratoires Théa have been able to bring together a pool of specialists and involved the various departments of the company (Research and Development, Regulatory Affairs, Quality Control...) in order to patent and to optimise the ABAK system, they are now busy partially internalising production of this system rather than favouring subcontracting it.

Each part of the device has been minutely thought out and developed resulting in multiple invention patents and the trend is therefore to internalise the knowledge, even if, for the time being, this internalisation remains incomplete.
Thus the Milan Farmila production site (a Laboratoires Théa property) has seen its activity increase over recent months. Its manufacturing line will have to be rapidly adapted to the limitations of batch size imposed by the various markets in which the ABAK system is present.

Currently, a manufacturing site must be capable of producing batches of 17.000 to 150.000 units to meet the needs of the company whilst adhering to a supply delay of 90 days between the order and its delivery.

V. Summary: ABAK is a bottle...

preservative-free

Designed to preserve the integrity of the eye

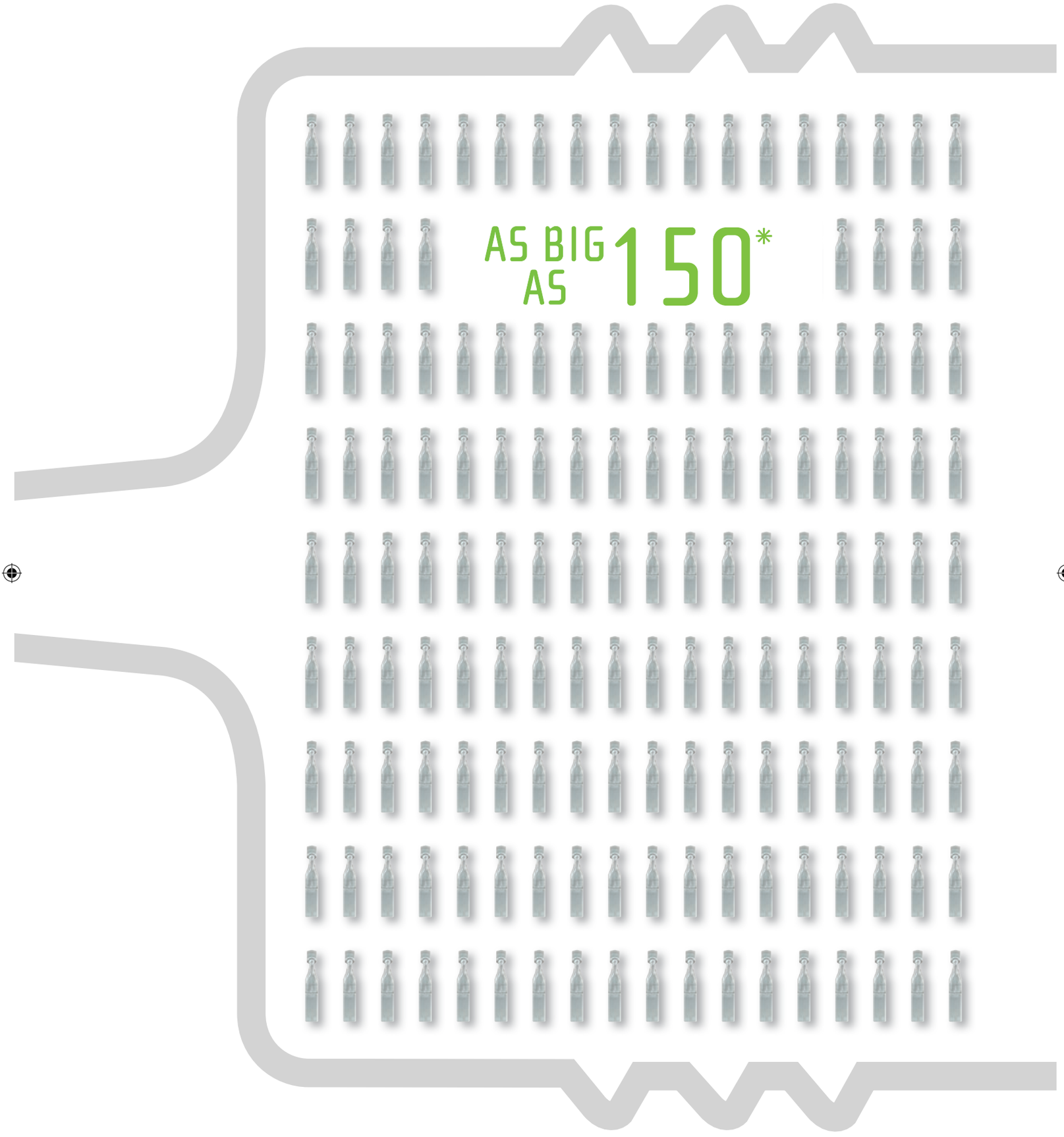
ergonomic

For everyone's hand

economic

AS SMALL AS
1 SINGLE-DOSE

*1 bottle of 10 ml = 300 drops
150 instillations for 2 eyes = 150 single-doses



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