Creation date : 04/12/03

Review date : 08/03/06

Document n°: CE/VOL/001/10

TECHNICAL FILE

VOLUMATIC™

PREPARATION

Department:	Name:	Signature:	Date:
NPS / STPack	S. Merlet		08/03/06

APPROVAL

Department:	Name:	Signature:	Date:
NPS / STPack	P. Huynh		08/03/06

INDEX

Presentation of Volumatic™

Intended Use of Volumatic™ Spacer Device

The Volumatic™ is a 750ml spacer device developed by GlaxoSmithKline for use with its range of inhalers. These inhalers deliver a range of medicinal products used in the treatment of respiratory diseases (Becloforte™, Becotide™, Flixotide™, Serevent™, Ventide™, Ventolin™, Seretide™). It is widely recognised that a considerable proportion of patients with obstructive lung disease have difficulty in co-ordinating the aerosol release of inhalers with inspiration. This dyscoordination results in a decrease in the amount of aerosol available for therapeutic effect in the airways, and a proportional increase in oral cavity deposition. Spacers are therefore designed to temporarily store discharged aerosol so that these effects are minimised when there is a delay between firing the inhaler and inhaling the stored aerosol cloud.

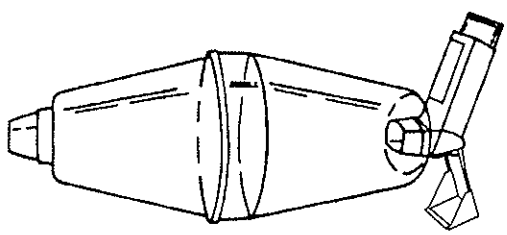
Clinical experience with large spacers of 750-1000ml volume indicate that they can increase the efficacy of bronchodilator therapy in dyscoordinated patients, while well-coordinated users showed only minor benefits.

The essential principles of spacer aerosol delivery have been demonstrated *in vitro* to measure the amount of aerosolised drug which could be withdrawn from the spacer into a Twin Impenger, type 2 (see In Vitro Evaluation Report in annex G). This two-stage separation device enabled the 'oropharyngeal' fraction (stage 1) and the 'pulmonary' fraction passing trough stage 1 (stage 2) to be measured separately. Simulated upper airway devices have been used to evaluate spacers in a similar manner. Results indicate that large or small volume spacers should give a marked reduction in oropharyngeal drug deposition but little change in the mass aerodynamic particle size distribution passing through the spacer.

General Description of Volumatic™ Spacer Device

The Volumatic™ Spacer Device is moulded from polycarbonate and is constructed and assembled from two main components; the actuator end and the mouthpiece end. The mouthpiece end is assembled from three components, the disk and ring are placed together to form the valve which is then inserted into the mouth end of the mouthpiece. The mouthpiece end, together with the one-way valve is integral with the mouthpiece-half of the chamber to avoid any possibility of inadvertent loss on detachment of either the mouthpiece or valve by the patient. The mouthpiece end and the actuator end fit together to form the Volumatic™ Spacer Device (see Annex C).

For the Paediatric Volumatic™ an additional component, the facemask, is supplied with the Volumatic™ Spacer Device described above. This facemask is moulded from silicone rubber and is attached to the mouth end of the mouthpiece half of the Volumatic™ prior to use. This will ensure that infants using the Volumatic™ will receive the full dose of drug, even through tidal breathing.



Annex B: Examples of artwork

Artwork and labeling of sales packaging (2 pages)

Patient information leaflet (3 pages)

Marking on device (1 page)

PHARMA CODE N° 8046

Volumatic™

ALLEN & HANBURYS

Volumatic™

Spacer Device

Tested and approved
for use with
Allen & Hanburys
Inhalers

Use as directed by your doctor

Please read the enclosed leaflet carefully before use

OVERPRINT AREA

BAR CODE AREA

5 000124 431204

D00002A
D00002A

ALLEN & HANBU

Voluma

Spacer De

Tested and app
for use wit
Allen & Hanb
Inhalers

PHARMA CODE N° 8

200mm measuring bar

EAT Phase II Artwork Information Panel for internally produced artwork	
Product Name	Volumatic Device
ECR	N/A
Item/Material Code	D00002A
Edge Code	NO
Cust. Ref. No.	8655 - 02/N/179
Drawing No.	01 325 01
Dimensions	100 x 100 x 169 mm
Varnish n°	N/A
Component type	Carton
Market	U.K.
Pharma/Mini Code	8046
Point of Sale Code	5000124431204
Scale	100 %
Colours (2)	Cutterguide n°325 Black Pantone 185 Pantone Pantone
Creation Date	12/11/2002
Operator's Name	Virginie CAHARD
Manufacturing Site	France (Evreux)
Replaces	N/A
Proof Number	P1/M1
Amended by	Name
Modification Date	00/00/2002
Proofreader's Check	----------
Date	----------

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2. Le design et les textes ne doivent pas être remaniés ou altérés.
   Les seules exceptions sont :
   a) Positionnement des edges codes
   b) Ajout logo imprimeur
   c) Repère patte à colle (PAC)
   d) N° de pose
3. Le fournisseur s'engagera à mettre en œuvre des méthodes de sécurité compatibles avec les impératifs ou les exigences de GlaxoSmithKline.
4. Après tout changement de version, les clichés doivent être détruits de façon à empêcher toute utilisation ultérieure.
5. Les disquettes, ZIP ou CD doivent être retournés au Service Conception Graphique.
6. En cas de problème, contacter le Service Conception Graphique.

MOALC46

& HANBURYS

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use with
& Hanburys
nhalers

Volumatic is a trademark of the Glaxo Wellcome Group of Companies ©1998

Allen & Hanburys
Stockley Park, Middlesex, UB11 1BT

CE

JHA937

HARMA CODE N° 8046

RÉFÉRENCE CATALOGUE VERSION A

Technical approval of artwork	
Name	
Position	S.T.A.C.
Accept	
Reject	
Date	
Signature	

200 mm

EAT Phase II Artwork Information Panel for internally produced artwork

Product name	Volumatic
ECR	N/A
Item/Material code	D00007A
Edge code	N/A
Cust. Ref. No.	B655-02/R/179
Drawing No.	02 032 01
Dimensions	382 x 140 mm
Varnish n°	N/A
Component type	Leaflet
Market	U.K.
Pharma/Mini Code	4647
Point of sale code	N/A
Scale	100 %

Colours (5)
- Black
- Cyan
- Magenta
- Pantone 185

Creation Date	14/11/2002
Operator's Name	Virginie CAHARD
Manufacturing site	France (Evreux)
Replaces	N/A
Proof Number	P1/M1
Amended by	Name
Modification Date	00/00/2002
Proofreader's Check	----------
Date	----------

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   c) Rajout partie à coller (PAC)
   d) N° de point
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Position	E.T.A.C.
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D00007A 14/11/02 16:00 Page 2

RECTO

8 Hold your breath, take the Volumatic out of your mouth and your finger from the top of the inhaler. Continue holding your breath for as long as is comfortable

9 Breathe out.

10 If you need to take more than one puff, remove the inhaler by tilting the top forward and repeat steps 3 to 9

11 After use, remove the inhaler from the Volumatic. Replace the mouthpiece cover to keep out dust and fluff

If you use more than one type of inhaler through the Volumatic repeat the process from step 2. There is no need to wait between inhalers.

If you find it difficult to press down on top of the inhaler when the Volumatic mouthpiece is in your mouth, you may fire a puff into the Volumatic and AT ONCE place the Volumatic mouthpiece in your mouth and breathe in (as in Step 7).

If you have been given different instructions for using your Volumatic device please follow them carefully.

Tell your doctor, nurse or pharmacist if you have any difficulties.

IS THERE ANYTHING I SHOULDN'T DO?

Don't squirt all your puffs into the Volumatic at once and then breathe them in. You must inhale one puff at a time.

Don't put your lips over the side holes of the mouthpiece, as the valve won't work.

Do not share your Volumatic with anyone, it should only be used by you.

CARE OF YOUR VOLUMATIC

Your Volumatic should be cleaned regularly, preferably twice a week.

1. Gently pull the two halves of the Volumatic apart. Do not take the valve apart
2. Wash the two halves of the Volumatic in warm water which can contain a mild detergent or a sterilising solution of the type used to clean babies' bottles. You can use a soft toothbrush or bottle brush to help remove any film which forms on the valve or the inside of the Volumatic. As long as the valve still moves when you breathe in and out, this deposit will not affect the working of the Volumatic.
3. Rinse thoroughly with clean water. Leave the parts at room temperature until they are completely dry. Don't rub the inside of your Volumatic with a cloth or polish as this may cause static electricity which can affect the inhaler. Don't put them in a heated place to dry more quickly.
4. Store the Volumatic in the carton to keep clean.

Children can often enjoy assembling their Volumatic and cleaning it as necessary under adult supervision. Stickers can be applied to the outside of the Volumatic as long as they do not interfere with the working of the device. They can practice making the valve rattle as they breathe in and out, without using the inhaler

A **Paediatric Volumatic** which has a soft face mask, is available for small children

Your Volumatic may need to be replaced after about 6 to 12 months of use.

200 mm

LEAFLET PREPARED SEPTEMBER 2002

ALLEN & HANBURYS

Allen & Hanburys
Stockley Park, Middlesex, UB11 1BT

PHARMA CODE N° 4647

ALLEN & HANBURYS

Volumatic™
Spacer Device

Tested and approved
for use with
Allen & Hanburys
Inhalers

CE

Please read this instruction leaflet
carefully before using
your **Volumatic** device

D00007A 11.2002

D00007A 14/11/02 16:00 Page 3

VERSO

-2-

WHAT IS A VOLUMATIC?

A Volumatic is a large-volume spacer device. It is used with Allen & Hanburys inhalers

WHAT IS THE VOLUMATIC USED FOR?

When using aerosol inhalers it is important that you release a puff of medicine just as you start to breathe in. The Volumatic helps you get the most from your inhaler. It allows more medicine to get down into your lungs where it is needed and less in your mouth where it can sometimes cause side-effects.

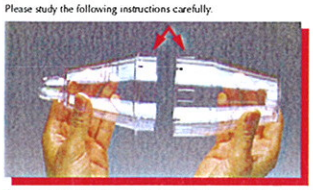
It is usually used:

- to overcome any difficulty with pressing the inhaler and breathing in at the same time.
- to give higher doses of medicine.

The Volumatic is intended for single patient use only.

HOW TO USE YOUR VOLUMATIC

Please study the following instructions carefully.



1 Fit the two halves of the Volumatic together. Line up the notch on one half with the slot on the other, then press together.

-3-

2 Take off the mouthpiece cover from the inhaler and check inside and outside to make sure that the mouth piece is clean.

If the inhaler is new or has not been used for a week or more, shake it well and release one puff into the air to prime it.

3 Shake the inhaler well

D00007A 11 2002

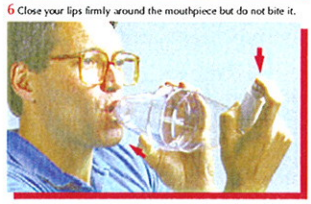
-4-

4 Fit the inhaler firmly into the end of the Volumatic, opposite the mouthpiece. Check the mouthpiece of the Volumatic inside and outside to make sure that it is clean.

5 Hold the device as shown. Breathe out as far as is comfortable and then ... ...

-5-

6 Close your lips firmly around the mouthpiece but do not bite it.



7 Press down with your finger(s) on the top of the inhaler to release one puff of medicine. Straightaway take one deep steady breath or 5 normal breaths to make sure that the medicine goes into your lungs. You do not need to take the Volumatic out of your mouth to breathe out. You should hear the mouthpiece valve 'click' or rattle as you breathe through it. If you don't hear it, tilt the Volumatic up slightly and try again.

200 mm

JAK004E

200mm measuring bar

EAT Phase II Artwork Information Panel for internally produced artwork

Product Name	Volumatic Volumatic Paediatric
ECR	N/A
Item/Material Code	D00003A (L0387GW)
Edge Code	N/A
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Drawing No.	18 001 01
Dimensions	40 x 50 mm
Varnish n°	N/A
Component type	Volumatic Printing (PAD)
Market	U.K.
Pharma/Mini Code	N/A
Point of Sale Code	N/A
Scale	100 %
Colours (1)	Cutterguide n° 001 Black Pantone Pantone Pantone
Creation Date	13/11/2002
Operator's Name	Virginie CAHARD
Manufacturing Site	France (Evreux)
Replaces	N/A
Proof Number	P1/M1
Amended by	Name
Modification Date	00/00/2002
Proofreader's Check	----------
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Date	
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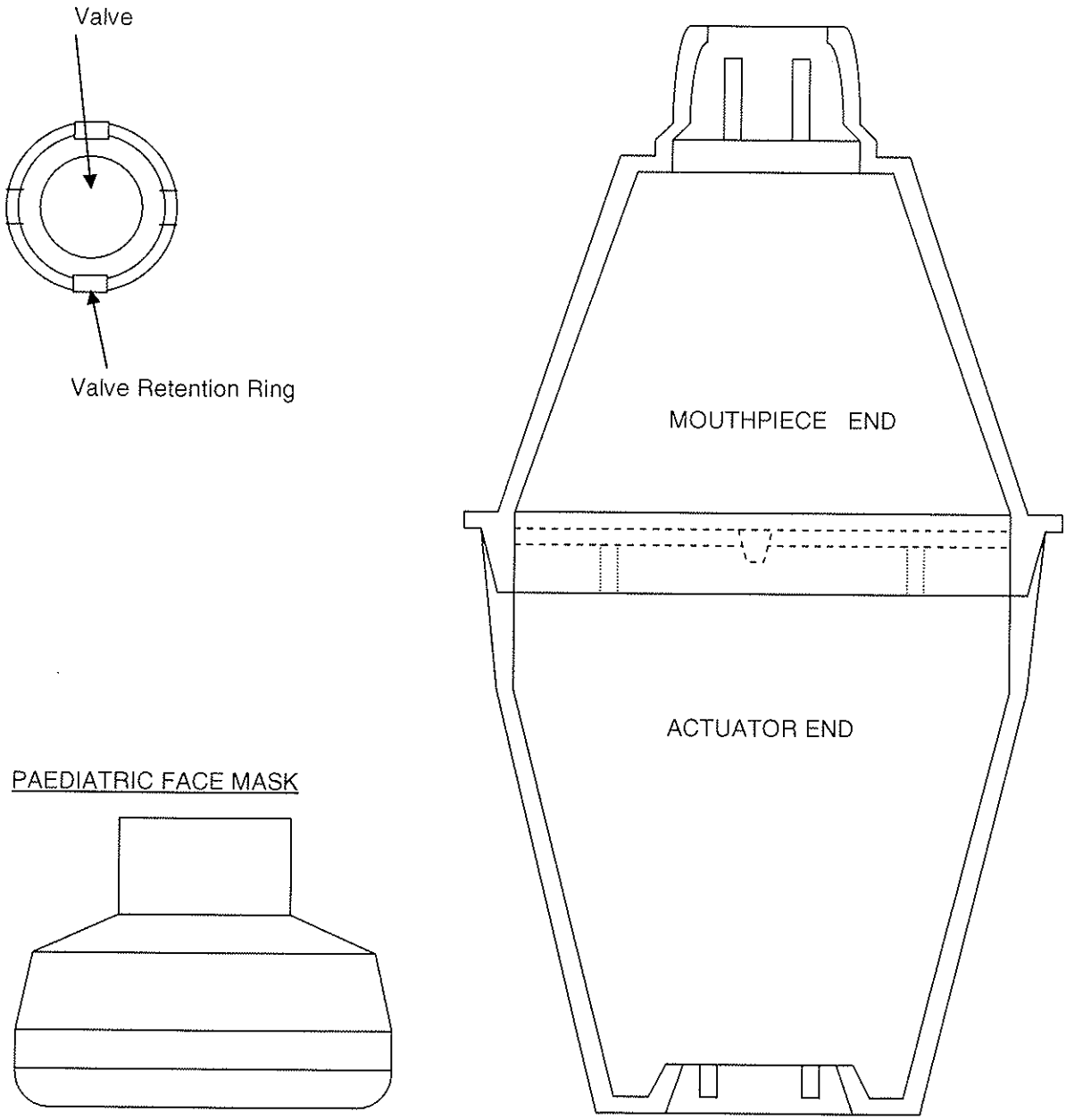
Annex C: General Schematic Drawing of Volumatic™ Spacer Device

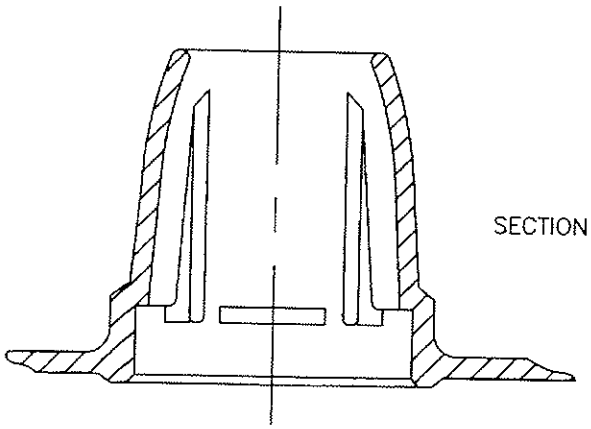
VOLUMATIC™ DEVICE



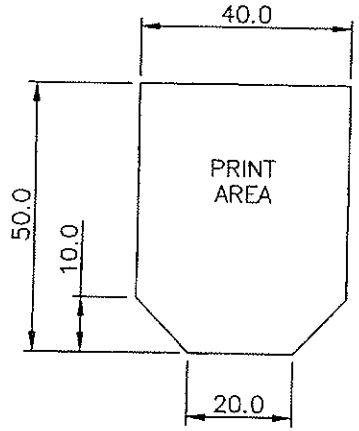
PAEDIATRIC FACE MASK

Component Name	Generic Material Name	Component Drawing N°
Mouthpiece End	Polycarbonate	JAK004
Actuator End	Polycarbonate	JAK004
Facemask	Silicone rubber	JAY002

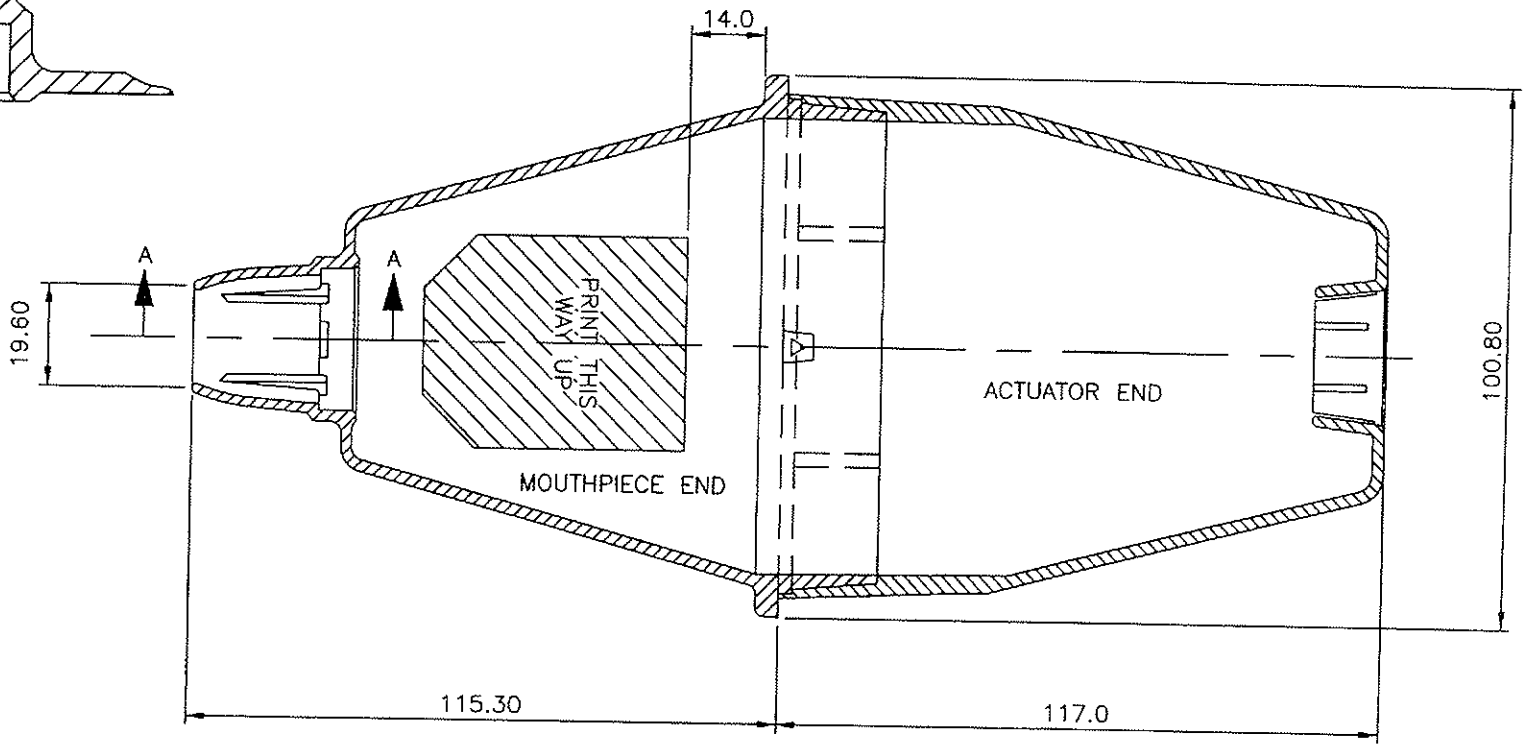
PRINT AREA
PLEASE NOTE.
ARTWORK TO FIT CONTOUR
OF DEVICE



SECTION A – A



WHEN APPLICABLE
CE MARK TO BE
POSITIONED CENTRALLY
WITHIN PRINT AREA
BELOW MARKET TEXT.



SHEET
1 OF 5

	WAS JAK002A AMENDMENTS DR.A3544–AP11 'SEE ARCHIVE DRAWINGS FOR PREVIOUS VERSIONS'	DATE AUTHORISED
B	SHEET 2, 14.95 ADDED – SECTION Y–Y. TO DR.A4349–AP11 20–8–93.	EMB.26–8–93
C	SHEET 2 :– SECTION X–X 17.55±0.1 WAS 17.83. PART SECTION 13.0 ADDED. VIEW ON ARROW 'A' 13.0 REF.ADDED. BEAD DETAIL ADDED. TO DR.B0322–AP11 3–5–95 NR	DEW.16–5–95
D	SHEET 4, 4.4+0.15/–0.25 WAS 4.4, ⌀26.5+0.05/–0.3 WAS ⌀26.5+0/–0.15 TO DR.1061–AP11 2–4–96 NR	ECW.10–4–96
E	SHEET.1 PRINT AREA ADDED STATEMENTS ADDED TO DR.B0052–AA20 3–11–97 NR	E.C.N. 02–11–97
1.0	PAGE 5 ADDED (CE CONFORMITY), CE/PRINT STATEMENT ADDED (PAGE 1). VERSION 1.0 UPDATED TO INTRODUCE NEW VERSION CONTROL. D1112–PG1300 08–03–2001 DS.	

TITLE
GENERAL ASSEMBLY OF VOLUMATIC SPACER MARK 4

PACKAGING TECHNOLOGY, GLAXOSMITHKLINE

	DRAWN	AUTHORISED
NAME	E.KENYON.	E.M.BEADLE
DATE	27–1–93	4–2–93

SCALE: N.T.S.

GENERAL TOLERANCE
UNLESS OTHERWISE STATED
±0.15 PER 25mm RUN

MATERIALS
POLYCARBONATE
: SEE MATERIAL SPECIFICATION

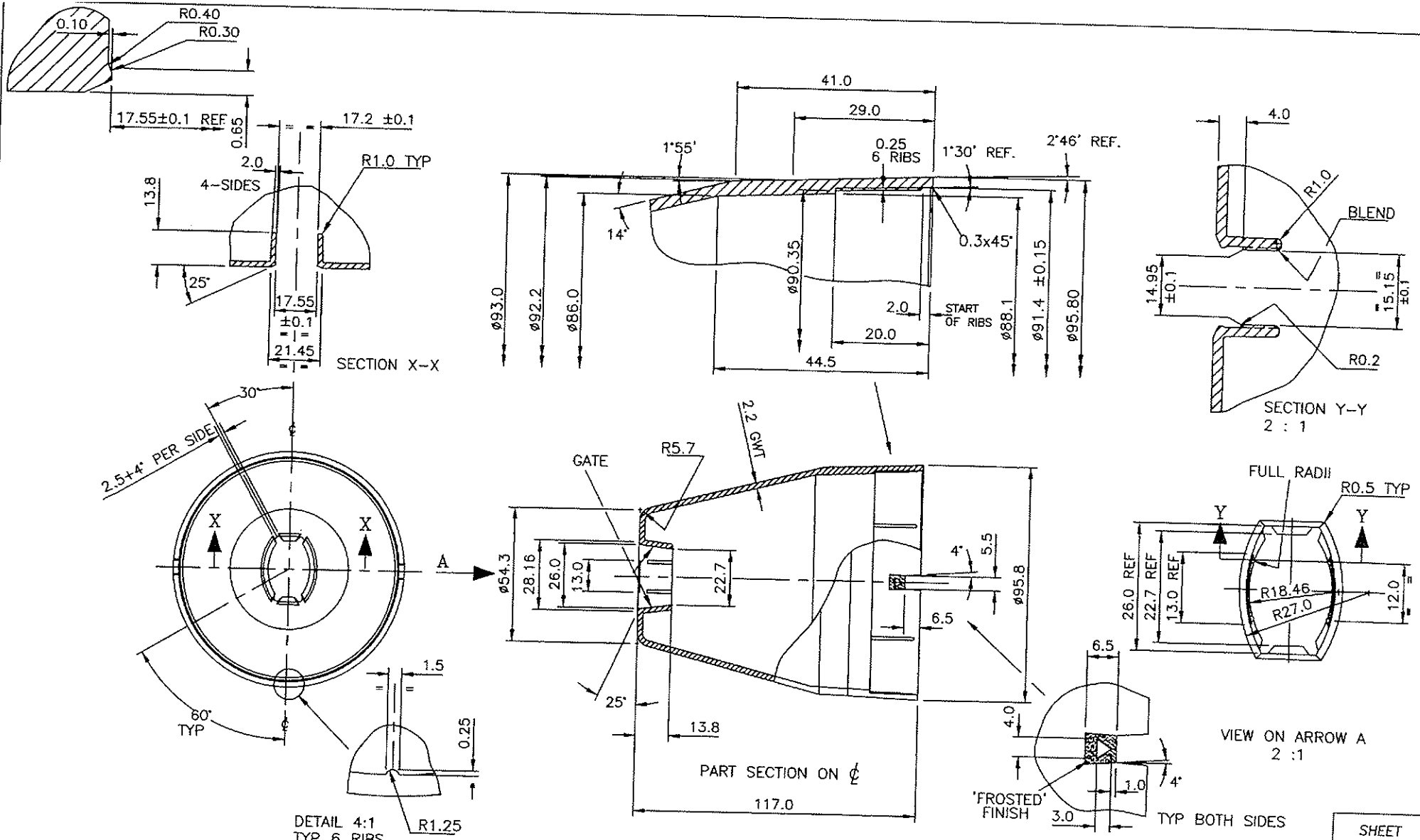
ALL DIMS. IN MILLIMETRES

THIRD ANGLE PROJ.

DO NOT SCALE

DRAWING NUMBER
JAK004

VERSION
1.0



SHEET 2 OF 5

TITLE: ACTUATOR END FOR VOLUMATIC SPACER MARK 4

PACKAGING TECHNOLOGY, GLAXOSMITHKLINE

PREVIOUS DRAWING NUMBER	SKK564		DRAWN	SCALE	GENERAL TOLERANCE UNLESS OTHERWISE STATED
DRAWING REQUEST	A3544	NAME	E.KENYON	N.T.S.	±0.15 PER 25mm RUN
		DATE	27-1-93		

MATERIALS: POLYCARBONATE : SEE MATERIAL SPECIFICATION

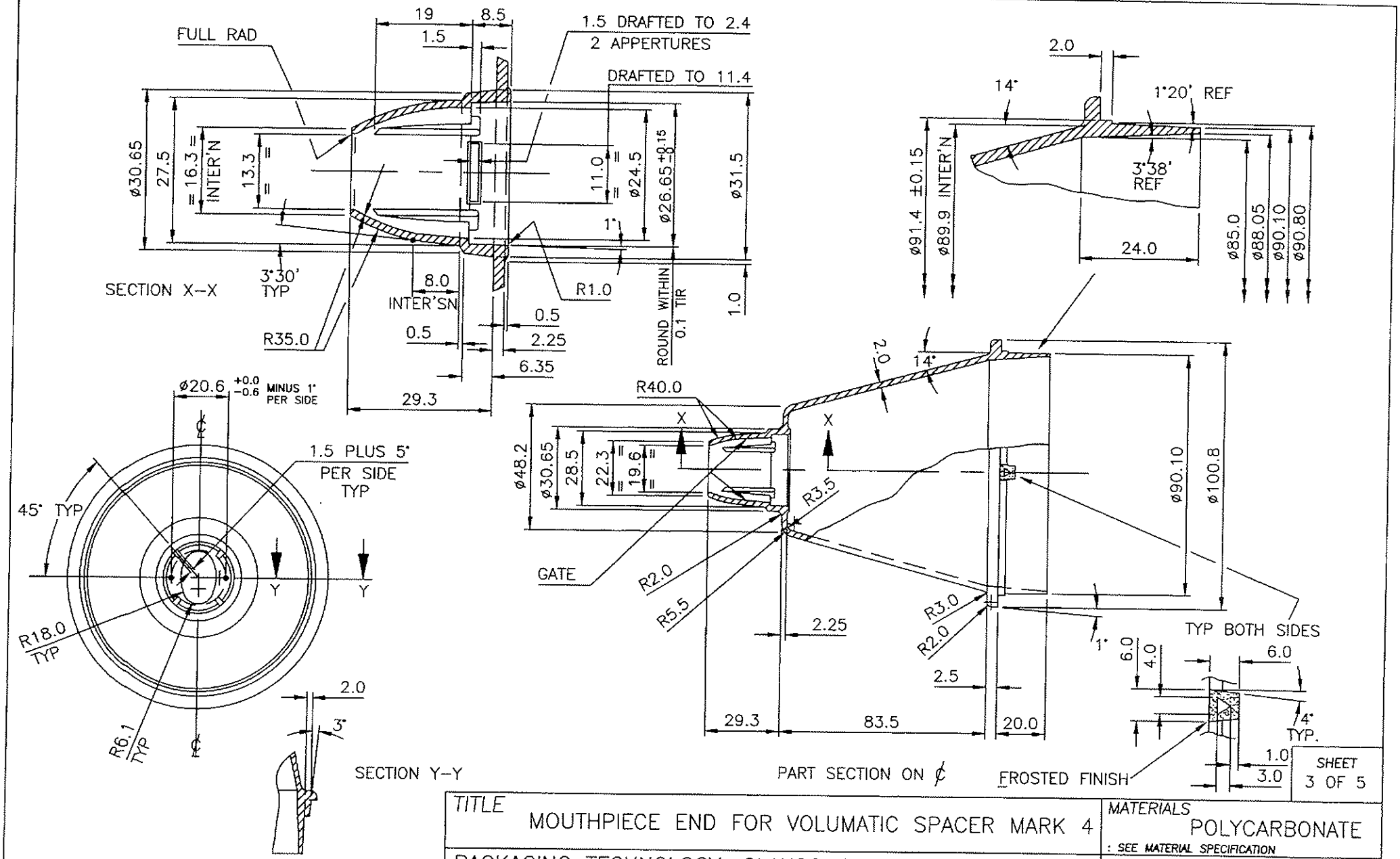
ALL DIMS. IN MILLIMETRES

THIRD ANGLE PROJ.

DO NOT SCALE

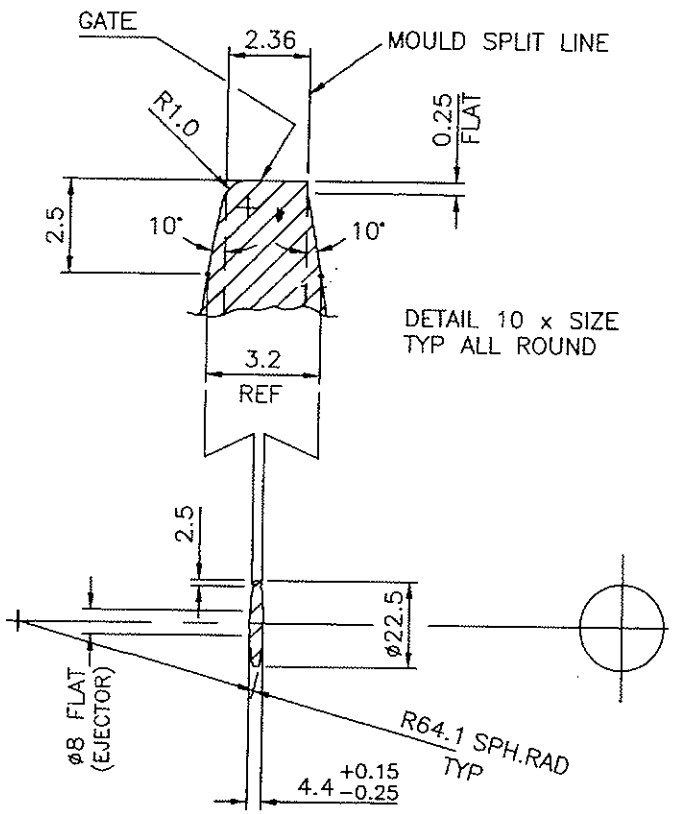
DRAWING NUMBER: JAK004

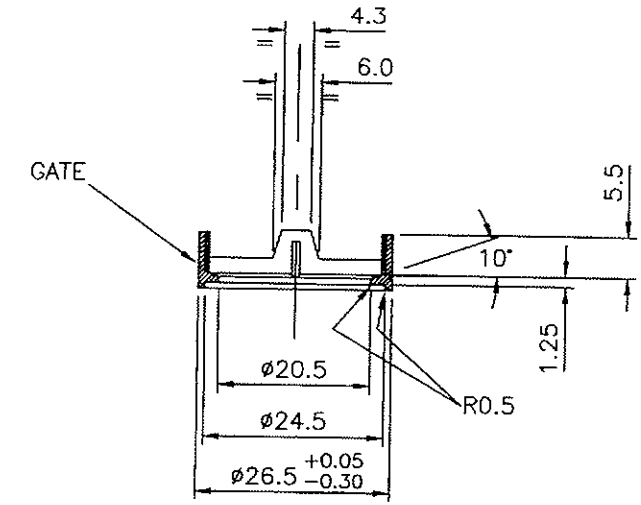
VERSION: 1.0

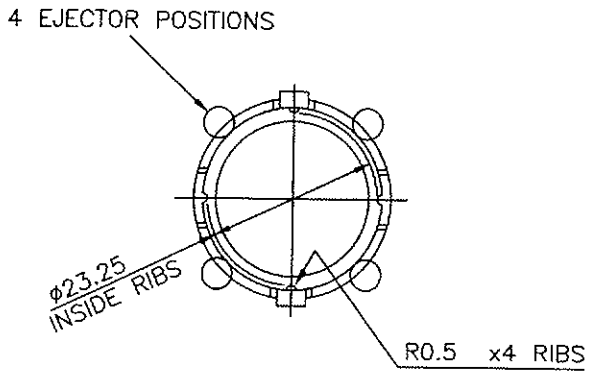


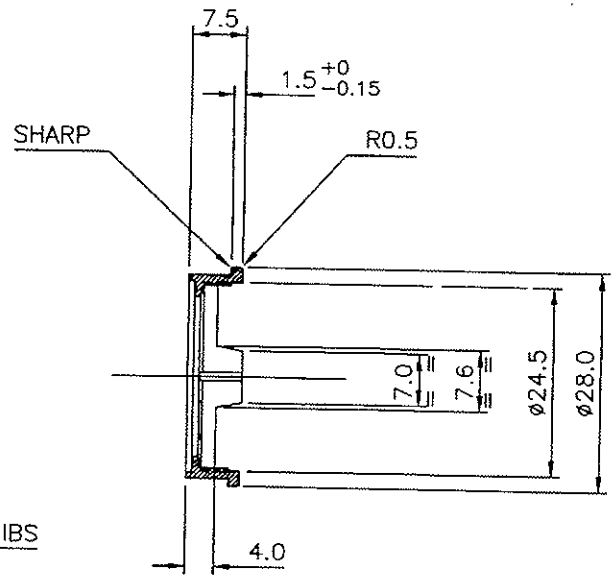
SHEET 3 OF 5

TITLE: MOUTHPIECE END FOR VOLUMATIC SPACER MARK 4						MATERIALS: POLYCARBONATE : SEE MATERIAL SPECIFICATION	
PACKAGING TECHNOLOGY, GLAXOSMITHKLINE						ALL DIMS. IN MILLIMETRES	
COPYRIGHT IS THE PROPERTY OF THE GLAXO GROUP OF COMPANIES						THIRD ANGLE PROJ.	
						DO NOT SCALE	
PREVIOUS DRAWING NUMBER	JAK002A		DRAWN	SCALE	GENERAL TOLERANCE UNLESS OTHERWISE STATED	DRAWING NUMBER	VERSION
DRAWING REQUEST	A3544	NAME	E.KENYON	N.T.S.	±0.15 PER 25mm RUN	JAK004	1.0
		DATE	27–1–93				









SHEET 4 OF 5

TITLE: VALVE DISC & VALVE DISC RETAINER FOR VOLUMATIC SPACER MK4						MATERIALS: POLYCARBONATE : SEE MATERIAL SPECIFICATION	
PACKAGING TECHNOLOGY, GLAXOSMITHKLINE						ALL DIMS. IN MILLIMETRES	
						THIRD ANGLE PROJ.	
						DO NOT SCALE	
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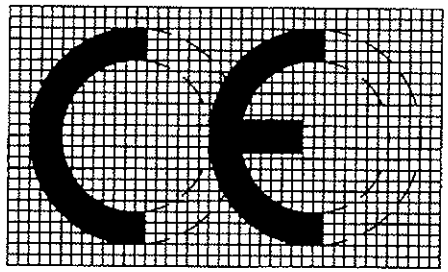
DRAWING REQUEST	A3544	NAME	E.KENYON	N.T.S.	±0.15 PER 25mm RUN	JAK004	1.0
		DATE	27-1-93				

CE MARKING OF CONFORMITY

THE CE CONFORMITY MARKING SHALL CONSIST OF THE INITIALS 'CE' TAKING THE FOLLOWING FORM:



–IF THE MARKING IS REDUCED OR ENLARGED THE PROPORTIONS GIVEN IN THE ABOVE GRADUATED DRAWING MUST BE RESPECTED.

– THE VARIOUS COMPONENTS OF THE CE MARKING MUST HAVE SUBSTANTIALLY THE SAME VERTICAL DIMENSION, WHICH MUST BE A MINIMUM OF 5mm

SHEET 5 OF 5

TITLE: VOLUMATIC SPACER CE MARK DIMENSIONS						MATERIALS: POLYCARBONATE (: SEE MATERIAL SPECIFICATION)	
PACKAGING TECHNOLOGY, GLAXOSMITHKLINE						ALL DIMS. IN MILLIMETRES	
COPYRIGHT IS THE PROPERTY OF THE GLAXO GROUP OF COMPANIES						THIRD ANGLE PROJ.	
						DO NOT SCALE	
PREVIOUS DRAWING NUMBER	N/APP.		DRAWN	SCALE	GENERAL TOLERANCE UNLESS OTHERWISE STATED	DRAWING NUMBER	VERSION
DRAWING REQUEST	D1112–PG1300	NAME	D.STEPHENSON	N.T.S.	±0.15 PER 25mm RUN	JAK004	1.0
		DATE	08–03–2001				

Annex D: DEPARTMENT OF HEALTH DEVICE CLASSIFICATION SYSTEM

CLASSIFY

Report prepared by: Charles Pilling, WWRA.

22nd February 2001

DEVICE: **VOLUMATIC™**

Company: **GlaxoSmithKline**

CONCLUSION **The device is CLASS I**

Questions answered:

Q 1 answered NO.

Is the device a blood bag?

Q 2 answered NO.

Does the device incorporate a medicinal product as an integral part?

Q 3 answered NO.

Is the device manufactured using animal tissue, or derivatives?

Q 4 answered NO.

Is the device intended to be used for contraception?

Q 4.1 answered NO.

Is the device intended for the prevention of sexually transmitted diseases?

Q 5 answered NO.

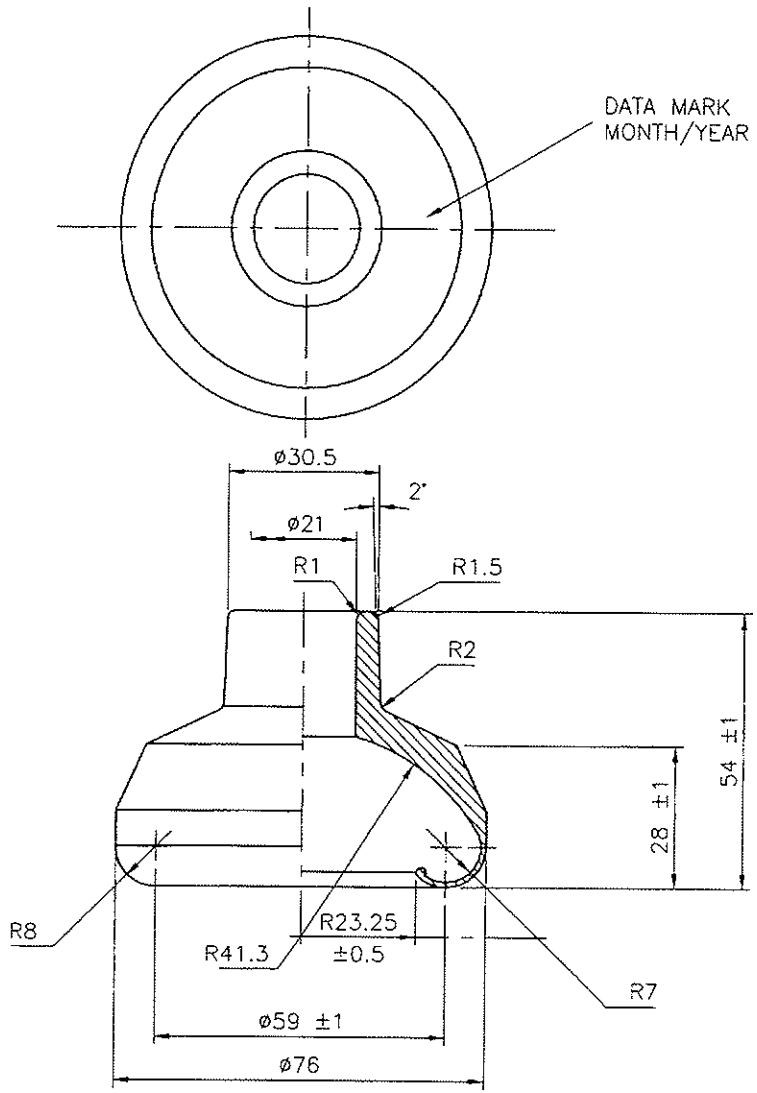
Is the device intended SPECIFICALLY for disinfecting, cleaning, rinsing or hydrating medical devices?

Q 6 answered NO.

Is it a non-active device intended SPECIFICALLY for recording X-ray diagnostic images?

Q 7 answered YES.

Is it a device which penetrates inside the human body?



WEIGHT 49 ±1gram

LAERDAL 11198 AMENDMENTS DR.A5013-AA20		DATE AUTHORISED
A	GEN.TOL. ±0.5 REMOVED. TO DR.A5049-AA20 1-4-93 EK.	EMB.1-4-93
B	DATE MARK MONTH/YEAR & WEIGHT 49±1g ADDED ø30.5 WAS ø30 R41.3 WAS R41 ø46.5±1 WAS ø58 ø76 WAS ø74 28±1 WAS 28 54±1 WAS 54 ø21 WAS ø21.3 DIMS. DELETED GEN.TOL. ADDED DR.B1341-MMcS20 27-1-97 NR	DEW.31-1-97
C	R1 WAS R2 R23.25±0.5 ADDED ø59±1 CORRECTED WAS ø46.5±1 TO DR.B1397-PG20 29-9-97 NR	

TITLE PAEDIATRIC FACE MASK No. 2

PACKAGING TECHNOLOGY, GLAXO OPERATIONS UK LTD

	DRAWN	AUTHORISED
NAME	E.KENYON.	E.M.BEADLE
DATE	3-2-93	26-2-93

SCALE 1=1

GENERAL TOLERANCE
UNLESS OTHERWISE STATED
DECIMALS ±0.5
ANGLES ±0.5°

MATERIALS
SILICONE
: SEE MATERIAL SPECIFICATION

ALL DIMS. IN MILLIMETRES

THIRD ANGLE PROJ.

DO NOT SCALE

DRAWING NUMBER
JAY002C

Annex E : CHECKLIST OF COMPLIANCE WITH ESSENTIAL REQUIREMENTS OF MEDICAL DEVICE DIRECTIVE

General requirements (13 pages)

Risk analysis (11 pages)

Q 8 answered NO.

Is it a device which is totally introduced into the human body by surgical intervention?

Q 8.1 answered NO.

Is it a device which replaces the epithelial surface or the surface of the eye by surgical intervention?

Q 9 answered NO.

Is it a device which is partially introduced into the human body by surgical intervention?

Q 10 answered NO.

Is it a device which penetrates inside the human body through the body surface?

Q 10.1 answered NO.

Is it a device which is intended to produce penetration of the body other than through an established body orifice?

Q 17 answered NO.

Is it a non-active device intended to be connected to an active medical device in Class II or III?

Q 17.1 answered NO.

Is it a device which is intended for continuous use of more than 30 days?

Q 17.2 answered NO.

Is it a device which is intended for continuous use for more than 60 minutes?

Q 28 answered NO.

Is it an active device?

Annex E: Checklist of Compliance with Essential Requirements of Medical Device Directive.

Company: GlaxoSmithKline	Product/Product Group: Medical Device			Description (s): Volumatic™ Spacer Device	
Checklist compiled by: A. Thomas Completed by : GSK Evreux Date: 10/03/05	A N/A	Relevant Standards - Ref. No; Date; Clause(s).		Basis for claiming compliance with ER's (Standards compliance/justification for points of non-compliance; Bench testing; Biological Safety; Clinical; Sales/Complaints history; Equivalence to other product(s) - all with reference to relevant Reports No.(s).	
Essential Requirement		"Horizontal"	"Vertical"	Compliance Assessment	Report Ref. No./Issue No. or date
I. General Requirements 1. The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.	A	ISO 14971-2000		Procedure for achieving CE marking on devices Risk Analysis Annual Product Review	CSOP/0030 Annex E Report of latest issue
2. The solutions adopted by the manufacturer for the design and construction of the devices must conform to safety principles, taking account of the generally acknowledged state of the art. In selecting the most appropriate solutions, the manufacturer must apply the following principles in the following order: – eliminate or reduce risks as far as possible (inherently safe design and construction), – where appropriate take adequate protection measures including alarms if necessary, in relation to risks that cannot be eliminated, – inform users of the residual risks due to any shortcomings of the protection measures adopted.	A	ISO 14971-2000		Risk Analysis Patient Information Leaflet, included in parts list for device	Annex E Annex B
3. The devices must achieve the performances intended by the manufacturer and designed, manufactured and packaged in such a way that they are suitable for one or more of the functions referred to in Article 1(2) (a), as specified by the manufacturer.	A			In Vitro Evaluation Report & Technical Memorandum on 5 year-old devices	GRW/84/0044-47 TM/PTS/98/0035
4. The characteristics and performances referred to in sections 1, 2, and 3 must not be adversely affected to such a degree that the clinical conditions and safety of the patients and, where applicable, of other persons are compromised during the lifetime of the device as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use.	A	ISO 14971-2000		Normal conditions of use in Patient Information Leaflet Risk Analysis Annual Product Review	Annex B Annex E Report of latest issue

Annex E: Checklist of Compliance with Essential Requirements of Medical Device Directive.

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Checklist compiled by: A. Thomas **Completed by : GSK Evreux** **Date: 10/03/05**	**A** **N/A**	**Relevant Standards - Ref. No; Date; Clause(s).**		**Basis for claiming compliance with ER's (Standards compliance/justification for points of non-compliance; Bench testing; Biological Safety; Clinical; Sales/Complaints history; Equivalence to other product(s) - all with reference to relevant Reports No.(s).**	
Essential Requirement		**"Horizontal"**	**"Vertical"**	**Compliance Assessment**	**Report Ref. No./Issue No. or date**
5. The devices must be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected during transport and storage taking account of the instructions and information provided by the manufacturer.	A	ISO 14971-2000 ISTA 2A		Risk Analysis Annual Product Review Transit tests	Annex E Report of latest issue Pira report dated Sept 2004
6. Any undesirable side-effect must constitute an acceptable risk when weighed against the performances intended.	A	ISO 14971-2000		Risk Analysis Annual Product Review	Annex E Report of latest issue
II. Requirements regarding Design and Construction **7. Chemical, Physical and Biological Properties** 7.1. The devices must be designed and manufactured in such a way as to guarantee the characteristics and performances referred to in Section I on the "General requirements". Particular attention must be paid to: – the choice of materials used, particularly as regards toxicity and, where appropriate, flammability; – the compatibility between the materials used and biological tissues, cells and body fluids, taking account of the intended purpose of the device;	A	ISO 14971-2000		Materials used in construction are non-toxic, non-flammable & their intended use is non-invasive & involves only intermittent contact. In Vitro Evaluation Report & Technical Memorandum on 5 year-old spacers Risk Analysis Precautions of use in the Patient Information Leaflet	GRW/84/0044-47 & TM/PTS/98/0035 Annex E Annex B
7.2. The devices must be designed, manufactured and packed in such a way as to minimise the risk posed by contaminants and residues to the persons involved in the transport, storage and use of the devices and to the patients, taking account of the intended purpose of the product. Particular attention must be paid to the tissues exposed and to the duration and frequency of exposure.	A			Procedure for final inspection & sampling in production Cleaning instructions in Patient Information Leaflet	Cahier des charges AC/0082 & AC/0087 Annex B

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Essential Requirement		**"Horizontal"**	**"Vertical"**	**Compliance Assessment**	**Report Ref. No./Issue No. or date**
7.3. The devices must be designed and manufactured in such a way that they can be used safely with the materials, substances and gases with which they enter into contact during their normal use or during routine procedures; if the devices are intended to administer medicinal products they must be designed and manufactured in such a way as to be compatible with the medicinal products concerned according to the provisions and restrictions governing these products and that their performance is maintained in accordance with the intended use.	A	ISO 14971-2000		Risk Analysis Washing instructions in Patient Information Leaflet In Vitro Evaluation Report & Technical Memorandum on 5 year-old devices	Annex E Annex B GRW/84/0044-47 & TM/PTS/98/0035
7.4. Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in Article 1 of Directive 65/65/EEC and which is liable to act upon the body with action ancillary to that of the device, the safety, quality and usefulness of the substance must be verified, taking account of the intended purpose of the device, by analogy with the appropriate methods specified in Directive 75/318/EEC.	N/A	75/318/EEC		Medicinal products used with the device are not integral & are subject to separate EP conformity assessment.	
7.5. The devices must be designed and manufactured in such a way as to reduce to a minimum the risks posed by substances leaking from the device.	A	ISO 14971-2000		Risk Analysis	Annex E
7.6. Devices must be designed and manufactured in such a way as to reduce, as much as possible, risks posed by the unintentional ingress of substances into the device taking into account the device and the nature of the environment in which it is intended to be used.	A	ISO 14971-2000		Risk Analysis	Annex E
8. **Infection and Microbial Contamination** 8.1. The devices and manufacturing processes must be designed in such a way as to eliminate or reduce as far as possible the risk of infection to the patient, user and third parties. The design must allow easy handling and, where necessary, minimise contamination of the device by the patient or vice versa during use.	A	ISO 14971-2000		Risk Analysis Cleaning procedures described in the Patient Information Leaflet	Annex E Annex B

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Essential Requirement		"Horizontal"	"Vertical"	Compliance Assessment	Report Ref. No./Issue No. or date
8.2. Tissues of animal origin must originate from animals that have been subjected to veterinary controls and surveillance adapted to the intended use of the tissues. Notified bodies shall retain information on the geographical origin of the animals. Processing, preservation, testing and handling of tissues, cells and substances of animal origin must be carried out so as to provide optimal security. In particular safety with regard to viruses and other transferable agents must be addressed by implementation of validated methods of elimination or viral inactivation in the course of the manufacturing process.	N/A			Device does not contain any tissue of animal origin.	
8.3. Devices delivered in a sterile state must be designed, manufactured and packed in a non-reusable pack and/or according to appropriate procedures to ensure that they are sterile when placed on the market and remain sterile, under the storage and transport conditions laid down, until the protective packaging is damaged or opened.	N/A			Device is not delivered sterile.	
8.4. Devices delivered in a sterile state must have been manufactured and sterilised by an appropriate, validated method.	N/A			Device is not delivered sterile.	
8.5. Devices intended to be sterilised must be manufactured in appropriately controlled (e.g. environmental) conditions.	N/A			Device is not intended to be sterilised.	
8.6. Packaging systems for non-sterile devices must keep the product without deterioration at the level of cleanliness stipulated and, if the devices are to be sterilised prior to use, minimise the risk of microbial contamination; the packaging system must be suitable taking account of the method of sterilisation indicated by the manufacturer.	A (packaging)			Risk Analysis Device packed in closed transport box & plastic bag	Annex E Cahier des charges AC/0082 & AC/0087
8.7. The packaging and/or label of the device must distinguish between identical or similar products sold in both sterile and non-sterile condition.	N/A			Only non-sterile version of the device exists.	

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Essential Requirement		**"Horizontal"**	**"Vertical"**	**Compliance Assessment**	**Report Ref. No./Issue No. or date**
9. **Construction and Environmental Properties** 9.1. If the device is intended for use in combination with other devices or equipment, the whole combination, including the connection system must be safe and must not impair the specified performances of the devices. Any restrictions on use must be indicated on the label or in the instructions for use.	A			Devices are recommended in the Patient Information Leaflet and on packaging to be used with GSK inhalers.	Annex B
9.2. Devices must be designed and manufactured in such a way as to remove or minimise as far as is possible: – the risk of injury, in connection with their physical features, including the volume/pressure ratio, dimensional and where appropriate ergonomic features, – risks connected with reasonably foreseeable environmental conditions, such as magnetic fields, external electrical influences, electrostatic discharge, pressure, temperature or variations in pressure and acceleration, – the risks of reciprocal interference with other devices normally used in the investigations or for the treatment given, – risks arising where maintenance or calibration are not possible (as with implants), from ageing of materials used or loss of accuracy of any measuring or control mechanism.	A	ISO 14971-2000		Risk Analysis	Annex E
9.3. Devices must be designed and manufactured in such a way as to minimise the risks of fire or explosion during normal use and in single fault condition. Particular attention must be paid to devices whose intended use includes exposure to flammable substances or to substances which could cause combustion.	A			Risk Analysis Flammable substances are not used with spacers.	Annex E
10. **Devices with a measuring function** 10.1. Devices with a measuring function must be designed and manufactured in such a way as to provide sufficient accuracy and stability within appropriate limits of accuracy and taking account of the intended purpose of the device. The limits of accuracy must be indicated by the manufacturer.	N/A			Clause 10 does not apply because the device has not any measuring function.	

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Essential Requirement		**"Horizontal"**	**"Vertical"**	**Compliance Assessment**	**Report Ref. No./Issue No. or date**
10.2. The measurement, monitoring and display scale must be designed in line with ergonomic principles, taking account of the intended purpose of the device.	N/A				
10.3 The measurements made by devices with a measuring function must be expressed in legal units conforming to the provisions of Council Directive 80/181/EEC, as last amended by Directive 89/617/EEC.	N/A				
11. **Protection Against Radiation** 11.1. **General** 11.1.1. Devices shall be designed and manufactured in such a way that exposure of patients, users and other persons to radiation shall be reduced as far as possible compatible with the intended purpose, whilst not restricting the application of appropriate specified levels for therapeutic and diagnostic purposes.	N/A			Clause 11 does not apply because the device does not generate any kind of radiation.	
11.2. **Intended Radiation** 11.2.1. Where devices are designed to emit hazardous levels of radiation necessary for a specific medical purpose the benefit of which is considered to outweigh the risks inherent in the emission, it must be possible for the user to control the emissions. Such devices shall be designed and manufactured to ensure reproducibility and tolerance of relevant variable parameters. 11.2.2. Where devices are intended to emit potentially hazardous, visible and/or invisible radiation, they must be fitted, where practicable, with visual displays and/or audible warnings of such emissions.	N/A N/A				
11.3. **Unintended Radiation** 11.3.1. Devices shall be designed and manufactured in such a way that exposure of patients, users and other persons to the emission of unintended, stray or scattered radiation is reduced as far as possible.	N/A				

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Essential Requirement		"Horizontal"	"Vertical"	Compliance Assessment	Report Ref. No./Issue No. or date
11.4. **Instructions**					
11.4.1. The operating instructions for devices emitting radiation must give detailed information as to the nature of the emitted radiation, means of protecting the patient and the user and on ways of avoiding misuse and of eliminating the risks inherent in installation.	N/A				
11.5. **Ionising Radiation**					
11.5.1. Devices intended to emit ionising radiation must be designed and manufactured in such a way as to ensure that, where practicable, the quantity, geometry and quality of radiation emitted and be varied and controlled taking into account the intended use.	N/A				
11.5.2. Devices emitting ionising radiation intended for diagnostic radiology shall be designed and manufactured in such a way as to achieve appropriate image and/or output quality for the intended medical purpose whilst minimising radiation of the patient and user.	N/A				
11.5.3. Devices emitting ionising radiation, intended for therapeutic radiology shall be designed and manufactured in such a way as to enable reliable monitoring and control of the delivered dose, the beam type and energy and where appropriate the quality of radiation.	N/A				
12. **Requirements for Medical Devices Connected to or Equipped with an Energy Source**				Clause 12 does not apply because the device is neither equipped nor connected to any energy source.	
12.1. Devices incorporating electronic programmable systems must be designed to ensure the repeatability, reliability and performance of these systems according to the intended use. In the event of a single fault condition (in the system) appropriate means should be adopted to eliminate or reduce as far as possible consequent risks.	N/A				
12.2. Devices where the safety of the patients depends on an internal power supply must be equipped with a means of determining the state of the power supply.	N/A				

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Essential Requirement		"Horizontal"	"Vertical"	Compliance Assessment	Report Ref. No./Issue No. or date
12.3. Devices where the safety of the patients depends on an external power supply must include an alarm system to signal any power failure.	N/A				
12.4. Devices intended to monitor one or more clinical parameters of a patient must be equipped with appropriate alarm systems to alert the user of situations which could lead to death or severe deterioration of the patient's state of health.	N/A				
12.5. Devices must be designed and manufactured in such a way as to minimise the risks of creating electromagnetic fields which could impair the operation of other devices or equipment in the usual environment.	N/A				
12.6. **Protection Against Electrical Risks** Devices must be designed and manufactured in such a way as to avoid, as far as possible, the risk of accidental electric shocks during normal use and in single fault condition, provided the devices are installed correctly.	N/A				
12.7. **Protection Against Mechanical and Thermal Risks**					
12.7.1. Devices must be designed and manufactured in such a way as to protect the patient and user against mechanical risks connected with, for example, resistance, stability and moving parts.	N/A				
12.7.2. Devices must be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from vibration generated by the devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.	N/A				
12.7.3. Devices must be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source, unless the noise emitted is part of the specified performance.	N/A				

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Essential Requirement		**"Horizontal"**	**"Vertical"**	**Compliance Assessment**	**Report Ref. No./Issue No. or date**
12.7.4. Terminals and connectors to the electricity, gas or hydraulic and pneumatic energy supplies which the user has to handle must be designed and constructed in such a way as to minimise all possible risks.	N/A				
12.7.5. Accessible parts of the devices (excluding the parts or areas intended to supply heat or reach given temperatures) and their surroundings must not attain potentially dangerous temperature under normal use.	N/A				
12.8. **Protection Against the Risks Posed to the Patient by Energy Supplies or Substances**					
12.8.1. Devices for supplying the patient with energy or substances must be designed and constructed in such a way that the flow-rate can be set and maintained accurately enough to guarantee the safety of the patient and of the user.	N/A				
12.8.2. Devices must be fitted with the means of preventing and/or indicating any inadequacies in the flow-rate which could pose a danger.	N/A				
Devices must incorporate suitable means to prevent, as far as possible, the accidental release of dangerous levels of energy from an energy and/or substance source.	N/A				
12.9. The function of the controls and indicators must be clearly specified on the devices.	N/A				
Where a device bears instructions required for its operation or indicates operating or adjustment parameters by means of a visual system, such information must be understandable to the user and, as appropriate, the patient.	N/A				

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Essential Requirement		**"Horizontal"**	**"Vertical"**	**Compliance Assessment**	**Report Ref. No./Issue No. or date**
13. **Information supplied by the Manufacturer** 13.1. Each device must be accompanied by the information needed to use it safely and to identify the manufacturer, taking account of the training and knowledge of the potential users. This information comprises the details on the label and the data in the instructions for use. As far as practicable and appropriate, the information needed to use the device safely must be set out on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging. If individual packaging of each unit is not practicable, the information must be set out in the leaflet supplied with one or more devices. Instructions for use must be included in the packaging for every device. By way of exception, no such instructions for use are needed for devices in Class I or Class IIa if they can be used safely without any such instructions.	A			Carton artwork & Patient Information Leaflet Patient Information Leaflet included in parts list for device	Annex B Cahier des charges AC/0082 & AC/0087
13.2. Where appropriate, this information should take the form of symbols. Any symbol or identification colour used must conform to the harmonised standards. In areas for which no standards exist, the symbols and colours must be described in the documentation supplied with the device.	N/A			No symbols are used with the device.	
13.3. The label must bear the following particulars: a) the name or trade name and address of the manufacturer. For devices imported into the Community, in view of their distribution in the Community, the label, or the outer packaging, or instructions for use, shall contain in addition the name and address of either the person responsible referred to in Article 14(2) or of the authorised representative of the manufacturer established within the Community or of the importer established within the Community, as appropriate; b) the details strictly necessary for the user to identify the device and the contents of the packaging; c) where appropriate, the word "STERILE";	A A N/A			Printed on carton & Patient Information Leaflet Device is not supplied sterile.	Annex B

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Essential Requirement		"Horizontal"	"Vertical"	Compliance Assessment	Report Ref. No./Issue No. or date
d) where appropriate, the batch code, preceded by the word "LOT", or the serial number,	A			Batch code is printed on carton.	
e) where appropriate, an indication of the date by which the device should be used, in safety, expressed as the year and month;	N/A			The use-by date is taken into account after the first use by the patient.	
f) where appropriate, an indication that the device is for single use;	N/A			The device is reusable.	
g) if the device is custom-made, the words "custom-made device";	N/A			The device is not custom-made.	
h) if the device is intended for clinical investigations, the words "exclusively for clinical investigations";	N/A			The device is not for clinical investigations.	
i) any special storage and/or handling conditions;	A			Children to be supervised by adults is indicated on the Patient Information Leaflet.	Annex B
j) any special operating instructions;	N/A			No special operating instructions necessary to use the device.	
k) any warnings and/or precautions to take;	A			Precautions in the Patient Information Leaflet	Annex B
l) year of manufacture for active devices other than those covered by e). This indication may be included in the batch or serial number;	N/A			Device is not active.	
m) where applicable, method of sterilisation.	N/A			Device is not supplied sterile.	
13.4. If the intended purpose of the device is not obvious to the user, the manufacturer must clearly state it on the label and in the instructions for use.	A			Intended use specified on packaging & in the Patient Instruction Leaflet.	Annex B
13.5. Wherever reasonable and practicable, the devices and detachable components must be identified, where appropriate in terms of batches, to allow all appropriate action to detect any potential risk posed by the devices and detachable components.	A			Batch codes of components are supplied on the Certificate of Analysis provided by the supplier.	Cahier des Charges AC/0082 & AC/0087

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Essential Requirement		**"Horizontal"**	**"Vertical"**	**Compliance Assessment**	**Report Ref. No./Issue No. or date**
13.6. Where appropriate, the instructions for use must contain the following particulars:					
a) the details referred to in section 13.3, with the exception of (d) and (e);	A				
b) the performances referred to in section 3 and any undesirable side-effects;	A				
c) if the device must be installed with or connected to other medical devices or equipment in order to operate as required for its intended purpose, sufficient details of its characteristics to identify the correct devices or equipment to use in order to obtain a safe combination;	A			Details are printed on packaging and/or in the Patient Information Leaflet.	Annex B
d) all the information needed to verify whether the device is properly installed and can operate correctly and safely, plus details of the nature and frequency of the maintenance and calibration needed to ensure that the devices operate properly and safely at all times;	A				
e) where appropriate, information to avoid certain risks in connection with implantation of the devices;	N/A			Device is not intended to be implanted.	
f) information regarding the risks of reciprocal interference posed by the presence of the device during specific investigations or treatments;	N/A			The device is not present during investigations or specific treatments.	
g) the necessary instructions in the event of damage to the sterile packaging and, where appropriate details of appropriate methods of re-sterilisation;	N/A			Device is not supplied sterile.	
h) if the device is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, packaging and, where appropriate, the method of sterilisation of the device to the re-sterilised, and any restriction on the number of reuses.	A			Cleaning instructions are described in the Patient Information Leaflet.	Annex B
Where devices are supplied with the intention that they be sterilised before use, the instructions for cleaning and sterilisation must be such that, if correctly followed, the device will still comply with the requirements in section I;	N/A			The device does not require sterilisation before use.	

Annex E: Checklist of Compliance with Essential Requirements of Medical Device Directive.

Company: GlaxoSmithKline	Product/Product Group: Medical Device			Description (s): Volumatic™ Spacer Device	
Checklist compiled by: A. Thomas **Completed by : GSK Evreux** **Date: 10/03/05**	**A** **N/A**	**Relevant Standards - Ref. No; Date; Clause(s).**		**Basis for claiming compliance with ER's (Standards compliance/justification for points of non-compliance; Bench testing; Biological Safety; Clinical; Sales/Complaints history; Equivalence to other product(s) - all with reference to relevant Reports No.(s).**	
Essential Requirement		**"Horizontal"**	**"Vertical"**	**Compliance Assessment**	**Report Ref. No./Issue No. or date**
i) details of any further treatment or handling needed before the device can be used (for example, sterilisation, final assembly, etc);	A			Use with inhalers is described in the Patient Information Leaflet.	Annex B
j) in the case of devices emitting radiation for medical purposes, details of the nature, type, intensity and distribution of this radiation.	N/A			Device does not emit any kind of radiation.	
The instructions for use must also include details allowing the medical staff to brief the patient on any contra-indications and any precautions to be taken. These details should cover in particular:					
k) precautions to be taken in the event of changes in the performance of the devices;	N/A				
l) precautions to be taken as regards exposure, in reasonably foreseeable environmental conditions, to magnetic fields, external electrical influences, electrostatic discharges, pressure or variations in pressure, acceleration, thermal ignition sources, etc;	N/A			No such environment is needed to use the device.	
m) adequate information regarding the medicinal product or products which the device in question is designed to administer, including any limitations in the choice of substances to be delivered;	A			Devices are recommended in the Patient Information Leaflet and on packaging to be used with GSK inhalers.	Annex B
n) precautions to be taken against any special, unusual risks related to the disposal of the device;	A			No such risks identified in the Risk Analysis	Annex E
o) medicinal substances incorporated into the device as an integral part in accordance with section 7.4.;	N/A			Medicinal substances are not an integral part of the device.	
p) degree of accuracy claimed for devices with a measuring function.	N/A			Device has no measuring function.	
14. Where conformity with the essential requirements must be based on clinical data, as in section I (6), such data must be established in accordance with Annex X.	N/A				

Step 3

Definition of the Potential Outcome Levels:

Negligible	The patient will hardly notice the defect.	Aesthetic damage on device
Minor	The patient becomes inconvenienced in using the device.	Less important reparable damage of device
Moderate	Reversible personal injury requiring medical intervention.	Reparable damage of device (25% of device value)
Serious	Personal injury requiring hospitalisation or minor irreversible injury.	Irreversible damage
Critical	Irreversible personal injury that might lead to patient death.	Device to replace

Definition of the Probability of Occurrence Levels:

Frequent	The hazardous situation appears even if the device has no defect.
Probable	The hazardous situation appears in case of defect of the device, but manufacturing controls or preventive maintenance can not eliminate the failure.
Occasional	The hazardous situation appears in case of incorrect use by the patient.
Rare	The hazardous situation appears in case of defect of the device, but manufacturing controls or preventive maintenance can eliminate the failure; or the failure can be detected before use by the patient.
Unlikely	The hazardous situation appears only in case of multiple failures of the device.

Definition of the Acceptability Levels:

4	Intolerable risk
3	Undesirable risk, tolerable only if its reduction is not realistic or the costs of risk reduction are too huge considering the device benefits.
2	Tolerable risk if risk reduction is > device benefits.
1	Neglectible risk

	Potential Outcome				
Probability of Occurrence	Critical	Serious	Moderate	Minor	Negligible
Frequent	4	4	3	3	2
Probable	4	3	3	2	2
Occasional	3	3	2	2	1
Rare	3	2	2	1	1
Unlikely	2	2	1	1	1

Step 7

Acceptability Levels for Residual Risks:

3, 4	To reduce
From 0 to 2	Acceptable
<0	Negligible

Device: Volumatic / Vent-ah-aler

Date: 18/11/2004

Step 1						
	Use Stages	Stage Reference	Quantitative Characteristic	Limits	Qualitative Characteristic	Limits
Intended Use (as specified on the leaflet)	Depacking	S1	Dimensions of the carton	large enough to take the device	Easy to open the box	can be opened by a child
		S2	Resistance of the carton	damaged because of bad storage conditions	Sealing of the bag	need of a tool to open the bag; unsealed bag
	Handling	S3	Weight of the device	device handled by one hand	Contact material/skin	allergic reaction
		S4			Finger residues - cleanliness	vision through the device
	Reading of instructions for use	S5			Understanding of instructions	clear sentences and explicit photos
	Assembly	S6	Force to assemble	slipping of the halves	Correct position	understanding of instructions
	MDI introduction	S7	Dimensions of the MDI retainer	see tolerances on drawings JAK004/JAK005	Blocking of the MDI	impossible; MDI falls
	Settlement in the mouth	S8	Biting force	breaking the mouthpiece	Contact material/mouth	allergic reaction
	Settlement on the mouth (with mask)	S9	Adaptation of the mask on young children	dimensions (diameter, depth)	Correct position	understanding of instructions
	MDI actuation	S10	Not required as actuator not dealt with here			
	Drug cloud propagation	S11	Volume of the chamber	see In Vitro Evaluation		
	Inhalation	S12	Flow	from 0 up to 12L/min	Valve movement	blocked valve
	Exhalation	S13	Flow	from 0 up to 12L/min	Valve movement	blocked valve
	Breathing in the device	S14	Number of inhalations	10 to 15 inhalations		
	Device off the mouth	S15				
	MDI off	S16			Deblocking of the MDI	impossible; MDI falls
	Disassembly	S17			Integrity of the device	no deterioration because of disassembling
		S18			Easy to disassemble	no need of a tool
	Rinsing	S19	Rinsing time	depends on the type of detergent	Quality of detergent	affect the material; can wash the drug
	Drying	S20			Place to dry	cleanliness
	Packing in plastic bag	S21	Dimensions of the plastic bag	205x302mm approximatively	Cleanliness of the bag	particles, residues in the bag
		S22			Resistance of the bag; solidity	punch on the bag
	Packing in carton	S23	Dimensions of the carton	10x10x16.5 cm	Resistance of the carton	no deterioration due to storage between use
	Valve cleaning (with a toothbrush)	S24			Hygiene	contamination by residues
	Device mobility	S25	Chock resistance	see supplier commercial sheet		
		S26	Obstruction	10x10x16.5 cm		

Device: Volumatic / Vent-ah-aler

Step 1						
	Use Stages	Stage Reference	Quantitative Characteristic	Limits	Qualitative Characteristic	Limits
Reasonably Foreseeable Misuse	MDI blocked in actuator end	S27	Dimensions of the actuator end	see dimensions and tolerances on drawings JAK004/JAK005	Position of the MDI	blocked while assembling or disassembling
	Incorrect assembly	S28	Tightness	loss of drug dose		
	No cleaning/rinsing	S29			Long-term consequence	overdose; stuck components (valve especially)
		S30			Drug reaction on the material	deterioration (release of additives...)
	Use of a wet device	S31	Increase in drug deposition	drug cloud incorporated to water drops		
	Shared device between patients	S32			Hygiene: cleaning of the mouthpiece	cross-infection
	Release of several doses at one time	S33			Quantity of drug delivered	overdose; too much deposition in the device
	Drying with a tissue	S34	Friction	quantity of electrostatic charges	Type of fabric	particles, residues in the device
	No packing after use	S35			Aesthetics	deterioration
		S36			Hygiene	infection, rogue components
	Cleaning in a dishwasher	S37	Temperature borne by the material	up to 280°C (melt T°)	Nature of detergent	affect to the material
	Inversion mouthpiece end/actuator end	S38	Force to assemble	broken end or MDI		
	Blocked valve	S39	Position of the valve	dimensions of the space between valve and ring/of the mouthpiece	Position in the mouth	blocking tongue, lips or teeth
	Sunlight/frost/heat exposure	S40			Ageing of the material	decrease of device life
	MDI introduced in mouthpiece end	S41	Force	broken end or MDI		
	Other	S42	All other misuses; no description can be done			

Date: 17/03/2005

Device: **Volumatic / Vent-ah-aler**

	Step 2			Step 3				Step 4
	Type of Hazard	Source	Stage Reference	Potential Outcome	Probability of Occurrence	Final Risk Evaluation	Comments	Necessity of Risk Reduction
	Energy							
1	Electricity	no						
2	Emitted Heat	no						
3	Mechanical Force	no					no spring or mechanical tension	
4	Ionizing Radiation	no						
5	Non Ionizing Radiation	no						
6	Electromagnetic Fields, Emission	no						
7	Moving Parts	valve - blocking of movement	S12; S13; S39	minor	rare	1		no
8	Inopportune Movement	detached MDI during use	S7; S16; S27	minor	unlikely	1		no
9	Suspended Masses	no						
10	Patient Support Device Failure	no					no supporting function of the device	
11	Pressure (Vessel Rupture)	drug container	S10				not required as ancillary device not per 93/42/EEC	
12	Acoustic Pressure	no						
13	Vibrations (during use)	no						
14	Vibrations (during transport)	handling during transport	S2	negligible	frequent	2		yes
	Biological							
15	Bioburden/bio-contamination	manufacture, storage, transport, use	S4; S8; S14; S15	minor	rare	1		no
16	Pyrogenicity	no						
17	Unintended Output of Bioactive Substances	material	S30	serious as effects unknown	probable	3		yes
18	Incorrect Formulation	material	S42	serious as effects unknown	rare	2		yes
19	Toxicity	potential ingestion of valve	S42				see 51	
20	Genotoxicity/Teratogenicity	no						
21	Allergenicity	see 23 & 15	S3; S8					

Device: **Volumatic / Vent-ah-aler**

Date: 17/03/2005

	Step 2			Step 3				Step 4
	Type of Hazard	Source	Stage Reference	Potential Outcome	Probability of Occurrence	Final Risk Evaluation	Comments	Necessity of Risk Reduction
22	Zytotoxicity	no						
23	Bio-incompatibility	cleaning, disinfection	S19; S30	minor	frequent	2		yes
24	Inability to Maintain Hygienic Safety	handling, usage	S4; S21; S24; S32; S36	minor	occasional	2		yes
25	(Cross-) Infection	handling, usage	S32	serious	occasional	3		yes
26	Mutagenicity	no						
27	Carcinogenicity	no						
28	Oncogenicity	no						
29	Degradation	use, ageing (see 84)	S35; S40					
	Environment							
30	Electromagnetic Fields, Induction	no						
31	Inadequate Supply of Power or Coolant	no						
32	Restriction of Cooling	no						
33	Storage or Usage Outside Prescribed Environmental Conditions	handling, usage, storage	S37; S40	moderate	occasional	2		yes
34	Incompatibility with Other Devices	non authorised drug delivery system	S7; S16; S27	serious	rare	2		yes
35	Waste Products or Device Disposal	disposal of drug container & packaging	S42	negligible on environment	frequent	2		yes
36	Emissions of Electromagnetic Interferences	no						
37	Susceptibility to Electromagnetic Interferences	no						
38	Accidental Mechanical Damage	playing children, pets...	S42	critical	occasional	3	see 50	yes
	Substance or Energy Release							
39	Electricity	no						
40	Radiation	no						
41	Volume	no						
42	Pressure	no						
43	Medical Gas Supply	no						
44	Anaesthesic Agents Supply	no						

Device: Volumatic / Vent-ah-aler

	Step 2			Step 3				Step 4
	Type of Hazard	Source	Stage Reference	Potential Outcome	Probability of Occurrence	Final Risk Evaluation	Comments	Necessity of Risk Reduction
	Use of the Medical Device							
45	Incorrect Use	unavailable or separated instructions for use	S5	serious as effects unknown	rare	2		yes
46	Human Error	unclear instructions for use	S5; S9				see 54	
47	Incorrect Identification	manufacture	S42	minor	rare	1		no
48	Insufficient Warning of Side Effects	insufficient drug leaflet					not required as ancillary device not per 93/42/EEC	
49	Inadequate Warning likely with re-use	unclear instructions for use	S5				see 54	
50	Loss of Mechanical Integrity	loose components, incorrect assembly	S6; S25; S28; S39	critical	probable	4		yes
51	Accidental Ingestion	functional failure (detached valve)	S42	critical	unlikely	4		yes
52	Reasonably Foreseeable Misuse	see 'device use'	from S27 to S42				see 23, 24, 25, 33, 38, 50, 67, 70, 71, 83, 98	
53	Incorrect Measurement	no						
54	Inadequate Instructions for Use	poor leaflet	S5; S9	serious as effects unknown	probable	3		yes
55	Unintended Movable Parts	no						
56	Use by Unskilled Personnel	unskilled user	S5; S33; S42	serious as effects unknown	occasional	3		yes
57	Sharp Edges or Points	design, manufacture	S3; S4; S8; S9	moderate	rare	2		yes
58	Incompatibility with Accessories	no						
97	Incompatibility between components	manufacture of parts	S6; S17; S28	serious	rare	2		yes
	Communication Device/User							
59	Lapses and Cognitive Recall Errors	no						
60	Incorrect Diagnosis	no						
61	Complex Control System	no						
62	Misrepresentation of Results	no						
63	Inadequacy of Performance Characteristics for the Intended Use	chamber volume, ventilation dead space and breathing	S11; S39	critical	probable	4		yes

Date: 17/03/2005

Device: Volumatic / Vent-ah-aler

	Step 2			Step 3				Step 4
	Type of Hazard	Source	Stage Reference	Potential Outcome	Probability of Occurrence	Final Risk Evaluation	Comments	Necessity of Risk Reduction
64	Technical Failure	manufacture, misuse	S12; S13; S42	critical	probable	4		yes
65	Judgement Failure	no						
66	Memorising Failure	no						
67	Slips and Blunders	unskilled user	S5	serious as effects unknown	occasional	3		yes
68	Violation of Instructions	intended misuse					not required	
69	Unclear Presentation of settings	no						
70	Unclear Information to Use the Device	too complicated instructions for use	S5	serious as effects unknown	occasional	3		yes
71	Incorrect Configuration	incorrect assembly	S7; S8; S9; S28; S38; S41	serious	occasional	3		yes
72	Unclear Device State	no						
73	Poor Mapping of Controls or Information	no						
74	Insufficient Visibility, Tactility or Audibility	no						
	Ageing, Maintenance							
75	Erroneous Data Transfer	no						
76	Lack of Specification of End of Device Life	poor leaflet	S42	moderate	probable	3		yes
77	Lack of Specification of Maintenance Checks	no						
78	Inexisting Maintenance Specification	no					see 79	
79	Inadequate Maintenance	cleaning - lack of information on leaflet	S20; S24; S29; S30; S34; S37	minor	occasional	2		yes
80	Loss of Integrity, Electric	no						
81	Loss of Integrity, Mechanical	assembly difficulties	S6; S17; S18; S28	serious	occasional	3		yes
82	Inadequate Packaging	design, construction, manufacture	S1; S2; S22; S23; S26	negligible	frequent	2		yes
83	Improper Re-use	inappropriate cleaning	S34; S37	serious	occasional	3		yes
84	Functional Deterioration Due to Ageing	ageing of the components	S40	serious	probable	3		yes

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Device: Volumatic / Vent-ah-aler

	Step 2			Step 3				Step 4
	Type of Hazard	Source	Stage Reference	Potential Outcome	Probability of Occurrence	Final Risk Evaluation	Comments	Necessity of Risk Reduction
	Other							
85	Incompatibility with Surgical Procedure	no						
86	Incorrect Output	handling, usage of drug delivery	S10				not required as ancillary device not per 93/42/EEC	
87	Ingress of Liquids	no						
88	Ingress of Dust, Particles, Insects	storage	S21; S24; S34; S36	minor	frequent	2	see 51 & 82	yes
89	Leakage of Liquids	no						
90	Magnetic Fields (MR)	no						
91	Electrostatic Charging/Charges	friction (transport, cleaning)	S34	serious	frequent	4		yes
92	Electrocautery	no						
93	Ultrasonic Imaging	no						
94	Ambient Pressure Storage/Transport	no						
95	Temperature Storage/Transport	storage, transport	S40	minor	frequent	2		yes
96	Humidity Storage/Transport	storage, transport	S31; S40	minor	frequent	2		yes
98	Cleaning in a dishwasher	cleaning	S37	minor	occasional	2		yes

Risk Management
Risk Evaluation

Date: 17/03/2005

Device: Volumatic / Vent-ah-aler

	Type of Hazard	Step 4	Step 5	Step 6					Step 7		Step 9	
		Necessity of Risk Reduction	Applied Protection Measures						Result	Residual Risks Evaluation	Other Hazards Generated	Comments on Residual & Additional Risks
			Description	Increase of detection	Reliability level	Decrease of exposure	Decrease of probability	Protection Measure Evaluation				
7	Moving Parts	no										
8	Inopportune Movement	no						0				
14	Vibrations (during transport)	yes	pack in a plastic bag to avoid abrasion	0	2	0	2	4	-2	negligible	yes, see 82	
15	Bioburden/bio-contamination	no										
17	Unintended Output of Bioactive Substances	yes	use approved materials	0	1	1	1	3	0	acceptable	no	FDA-approved 'medical grade' material
18	Incorrect Formulation	yes	check the material before manufacturing	1	1	2	1	5	-3	negligible	no	
23	Bio-incompatibility	yes	design for easy cleaning & provide information in instructions for use	2	2	1	2	7	-5	negligible	yes, see 54	
24	Inability to Maintain Hygienic Safety	yes	describe cleaning & disinfection procedure in instructions for use	2	0	1	0	3	-1	negligible	yes, see 54	see 23
25	(Cross-) Infection	yes	provide warning not to be used by an other patient in instructions for use	2	0	1	0	3	0	acceptable	no	
33	Storage or Usage Outside Prescribed Environmental Conditions	yes	use a resistant material (temperature, humidity)	0	2	0	2	4	-2	negligible	no	
34	Incompatibility with Other Devices	yes	mechanical coding & warning in instructions for use	2	2	2	2	8	-6	negligible	no	
35	Waste Products or Device Disposal	yes	use an environment-friendly material	0	2	0	2	4	-2	negligible	no	
38	Accidental Mechanical Damage	yes	provide warning in instructions for use not to let children play with the device unsupervised	2	0	1	0	3	0	acceptable	no	
45	Incorrect Use	yes	include instructions for use in parts list for device and check for completeness in final inspection	0	1	1	1	3	-1	negligible	no	use of device simple once understood

Date: 17/03/2005

Device: Volumatic / Vent-ah-aler

	Type of Hazard	Step 4	Step 5	Step 6					Step 7		Step 9	Comments on Residual & Additional Risks
		Necessity of Risk Reduction	Applied Protection Measures						Result	Residual Risks Evaluation	Other Hazards Generated	
			Description	Increase of detection	Reliability level	Decrease of exposure	Decrease of probability	Protection Measure Evaluation				
47	Incorrect Identification	no										
50	Loss of Mechanical Integrity	yes	describe assembly & control of the functioning in instructions for use	2	0	1	0	3	1	acceptable	yes, see 54	
51	Accidental Ingestion	yes	mouthpiece dimensions < valve dimensions so that the valve could not enter the mouth	0	2	2	2	6	-2	negligible	no	
54	Inadequate Instructions for Use	yes	provide adequate instructions for use (nomenclature to check)	1	1	1	1	4	-1	negligible	no	
56	Use by Unskilled Personnel	yes	provide statement to read and understand instructions for use	2	0	1	0	3	0	acceptable	no	
57	Sharp Edges or Points	yes	design to minimise	1	2	1	2	6	-4	negligible	no	
97	Incompatibility between components	yes	check tolerances of components to fit with each other	1	1	2	1	5	-3	negligible	no	
63	Inadequacy of Performance Characteristics for the Intended Use	yes	minimise ventilation dead space through valve; only discontinuous use to be prescribed	0	2	2	2	6	-2	negligible	no	
64	Technical Failure	yes	design the valve for robustness & provide a statement on how to control the functioning of the valve	2	2	1	2	7	-3	negligible	no	
67	Slips and Blunders	yes	provide instructions for use	2	1	1	1	5	-2	negligible	yes, see 54	
70	Unclear Information to Use the Device	yes	provide explicit photos and schemes in instructions for use	2	0	2	0	4	-1	negligible	yes, see 67	
71	Incorrect configuration	yes	provide explicit photos and schemes in instructions for use	2	0	1	0	3	0	acceptable	no	
76	Lack of Specification of End of Device Life	yes	use durable materials & provide a sentence on replacement of device in instructions for use	2	2	1	2	7	-4	negligible	no	

Date: 17/03/2005

Device: Volumatic / Vent-ah-aler

	Type of Hazard	Step 4	Step 5	Step 6					Step 7		Step 9	Comments on Residual & Additional Risks
		Necessity of Risk Reduction	Applied Protection Measures						Result	Residual Risks Evaluation	Other Hazards Generated	
			Description	Increase of detection	Reliability level	Decrease of exposure	Decrease of probability	Protection Measure Evaluation				
79	Inadequate Maintenance	yes	describe cleaning & disinfection procedure in instructions for use	2	0	1	0	3	-1	negligible	yes, see 54	maintenance by the user
81	Loss of Integrity, Mechanical	yes	design to lock the parts each into the other	1	2	2	2	7	-4	negligible	yes, see 57	
82	Inadequate Packaging	yes	provide adequate packaging for transport	0	2	2	2	6	-4	negligible	no	
83	Improper Re-use	yes	describe cleaning & disinfection procedure in instructions for use	2	0	1	0	3	0	acceptable	yes, see 54	
84	Functional Deterioration Due to Ageing	yes	use durable materials & provide a sentence on replacement of device in instructions for use	2	2	2	2	8	-5	negligible	no	
88	Ingress of Dust, Particles, Insects	yes	provide sealed transport packaging & use a clear material	1	2	2	2	7	-5	negligible	yes, see 82	
91	Electrostatic Charging/Charges	yes	use plastic bag in packaging & provide a sentence not to clean with a tissue	2	1	1	1	5	-1	negligible	no	
95	Temperature Storage/Transport	yes	use a resistant material	0	2	0	2	4	-2	negligible	yes, see 23	
96	Humidity Storage/Transport	yes	use a resistant material	0	2	0	2	4	-2	negligible	yes, see 23	
98	Cleaning in a dishwasher	yes	provide warning in instructions for use not to clean in a dishwasher	2	0	1	0	3	-1	negligible	no	

Annex F : CHANGE CONTROL HISTORY FORM

CE/VOL/001/10

Date	Nature of Change	Technical File Reference
08/03/00	Certificate number at the bottom of each page changed from no.1 to 001/03. German Drawings and Location added German Suppliers listed. Change control History form added and pages renumbered accordingly.	CE/VOL/001/03
30/03/01	Annual review. Name change to GlaxoSmithKline. Page 1, Declaration of Conformity, " Plants of Manufacturer" addition of GSK, Aranda address. Annex D, correction to Answer 7. Does not affect the classification. Annex E, Procedure reference numbers updated as follows: Local GSK, Speke Packaging Procedures: P/GEN/035 replaced by P/GEN/085 P/GEN /039 replaced by P/GEN/ 043, 046 and 112 P/GEN/050 and 051 replaced by P/GEN/099 P/GEN/038 deleted, as not known.	CE/VOL/001/04
30/03/02	Annual review. Update Company address. Complaints History Review Report reference changed to SQA 02/042. All Speke device complaints are now summarised in one document. Speke Packaging Procedure reference P/GEN120 -Prepare, Release of Process order within the Packaging Area, added to Speke procedures Appendix 1 Supplier assessment and Manufacturing Procedure updated to QA/SQM/007	CE/VOL/001/05
30/03/02	Spanish address removed from "Plants of Manufacturer". They now source through Speke. Italy address has been added. They are direct sourcing from the UK supplier and controlling the artwork and packaging of the device. Addition of Competent Authority address to Appendix 1	CE/VOL/001/05
04/12/02	Update to first page of Declaration of Conformity, clarifying that "Plants of Manufacturer " are members of the GlaxoSmithKline group of companies.	CE/VOL/001/06
03/02/03	Update to first page of Declaration of Conformity, clarifying that "Plants of Manufacturer " are members of the GlaxoSmithKline group of companies.	CE/VOL/001/07
03/12/03	Document exploded in different files. Introduction presentation created in a main document. Update to general specifications for GlaxoSmithKline Evreux.	CE/VOL/001/08

CE/VOL/001/10

Date	Nature of Change	Technical File Reference
22/03/05	Introduction of a Risk Analysis following ISO 14971 standard. Update of the Essential Requirements Checklist to local GSK Evreux documents. Introduction of GPE plans.	CE/VOL/001/09
08/03/06	The supplier has been changed. Betts have been replaced by Nypro. Appendixes of risk analysis have been removed as they were working files.	CE/VOL/001/10

Annex G: Pharmaceutical evaluation

GRW/84/044-47
In Vitro Evaluation of a 750mL spacer in conjunction with Becotide inhaler and Ventolin inhaler
(24 pages)

TM/PTS/98/0035
Comparison of Volumatic™ inhalation spacer devices of different ages
Dated 29 Jan, 1998
(9 pages)

In Vitro evaluation of a 750ml Spacer in conjunction with Becotide Inhaler and Ventolin Inhaler

(notification submitted to the DHSS)

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UB6 0HB

1. INTRODUCTION

In recent years it has become increasingly recognised that a considerable number of patients with obstructive lung disease have difficulty in coordinating the aerosol release of metered dose inhalers (MDI) with inspiration. This was demonstrated convincingly in a recent study on 1173 hospital out-patients, where 51% were observed to have coordination difficulties (Crompton, 1982). One approach to this dyscoordination problem is to interpose an expansion chamber between the aerosol actuator mouthpiece and the patient's mouth to receive and temporarily store the discharged aerosol. Such devices have become widely known as spacers. They allow retardation of the high velocity spray and some delay between firing the inhaler and inhaling the stored aerosol cloud. A recent review of clinical experiences with large spacers of 750 - 1000ml volume shows that they can increase the efficacy of bronchodilator therapy in patients who are dyscoordinated with MDI's, but generally show little benefit in patients who are well-coordinated users (Weeke, 1982). In addition, some recent clinical studies show that bronchodilator drug aerosols delivered from a large spacer can be as effective as those from nebulisation of aqueous solutions.

The essential principles of spacer aerosol delivery with continuous airflow were demonstrated in vitro by Hallworth and Andrews (1976). Their results indicated that large or small spacers should give a marked reduction in oropharyngeal drug deposition but little change in the mass aerodynamic particle size distribution passing through the spacer. The quantity of aerosolised drug delivered through a model throat was similar for MDI's with or without a large spacer, but was reduced considerably with small spacer tubes. Moren (1978) measured the mouth and spacer deposition of bronchodilator aerosols in healthy volunteers after firing a MDI into a small (80ml) or large (1000ml) spacer. A deep inspiration was commenced either immediately or 5 seconds after firing the aerosol. The experiments with delayed inhalation were intended to represent the situation which would aid coordination. They showed a moderate increase (55 to 63%) in drug likely to pass beyond the mouth from the large spacer but a reduction (55 to 45%) with a small spacer. Both sizes of spacer caused a marked reduction in oral deposition.

Gamma camera studies in asthmatic patients with MDI's containing radiolabelled 'model' spherical Teflon particles have demonstrated some increase in drug deposition on the conducting airways of the lungs from MDI's delivered from a spacer with a large reduction in oropharyngeal deposition (Newman et al, 1981).

2. DESCRIPTION OF SPACER

The spacer, 750 ml volume, is moulded in two halves from polycarbonate. The mouthpiece together with the one-way valve is integral with the mouthpiece half of the chamber to avoid any possibility of inadvertant loss on detachment of either the mouthpiece or valve by the patient. A centre-line sectional longitudinal view of the spacer is provided in figure 1 and an exploded view showing it in its assembled and packed arrangements can be seen in figure 2.

3. IN VITRO EVALUATION OF THE SPACER

The performance of the new spacer was assessed by measuring the amount of aerosolised drug which could be withdrawn from the spacer into a Twin Impinger, type 2. This two-stage separation device enabled the 'oropharyngeal'fraction (Stage 1) and the 'pulmonary' fraction passing through Stage 1 (Stage 2) to be measured separately. Simulated upper airway devices have been used by Sciarra et al (1978) and Sackner et al (1981) to evaluate spacers in a similar manner.

The use of the older type 1 Twin Impinger for the assessment of fine particle delivery from metered dose inhalers has been described previously for beclomethasone dipropionate and salbutamol (submissions to the CSM for Ventide Inhaler (June, 1980) and Becloforte Inhaler (December, 1981). The use of the newer Twin Impinger type 2 to evaluate a range of commercial inhalers has been described by Meakin and Stroud (1983) and the relationship of its results to the clinical efficacy of a bronchodilator aerosol product by Padfield et al (1983).

The experiments were designed to evaluate:

1) The effect of collecting single shots in the spacer before withdrawal of aerosol.

2) The effect of accumulating multiple shots in the spacer before withdrawal of aerosol.

3) Flow behaviour of the spacer valve and exhalation hole.

3.1 Preparation of the test system

a) The can was removed from the actuator, the label was removed with chloroform and the can was cleaned with methanol. The actuator was replaced.

b) Two priming shots were fired.

c) The can was reweighed, then ten shots were fired to air in a fume cupboard, shaking the can for 30 seconds between each shot.

d) The exterior valve stem and actuator were cleaned inside and out with methanol, as was the exterior of the can.

e) The can was dried and reweighed, then fitted with the actuator.

The Twin Impinger was prepared for use before each experiment by placing 7ml and 30ml of methanol in the upper stage 1 flask and lower stage 2 flask respectively. The apparatus was assembled and connected via the lower side arm to a portable dust sampler pump, model L100 (Rothercoe and Mitchell Ltd.), set to draw air through the apparatus at 60 litres per minute. The Twin Impinger was coupled to the aerosol actuator during each experiment with a moulded silicone rubber adaptor which located on the inside and outside of the impinger inlet throat. This ensured correct centring and reproducible positioning of the actuator and an airtight seal. The arrangement is illustrated in Figure 3.

Before initial use the spacers were each washed with water, then with methanol and finally dried with warm air.

3.2 Procedure for firing the aerosols and collecting the analytical samples.

3.2.1 Evaluation of the effect of collecting single shots in the spacer before withdrawal of aerosol.

For each of the two products 10 aerosol cans, designated a - j, were each tested with an individual spacer, these being designated 1 - 10. Then the same cans were each tested with spacer number 10. The following procedure was followed for the measurement of each can/-spacer combination.

a) The can/actuator unit was shaken for 30 seconds and then inserted into the spacer mouthpiece socket, the spacer having been previously coupled to the Twin Impinger.

b) A series of 10 shots (Numbers 13 - 22) were fired into the spacer. Before each shot the can was shaken for 30 seconds and after each shot the Twin Impinger vacuum pump was switched on for 10 seconds after observing a 2 second delay and then switched off.

c) The can was removed from the spacer and reweighed.

d) The accumulated drug deposition in the actuator/spacer, stage 1 and stage 2 were each washed out with several aliquots of methanol and the washings of each were combined in separate 100ml volumetric flasks. The actuator/spacer sample included washings from the inside and outside of both the actuator and the external valve stem of the metering valve.

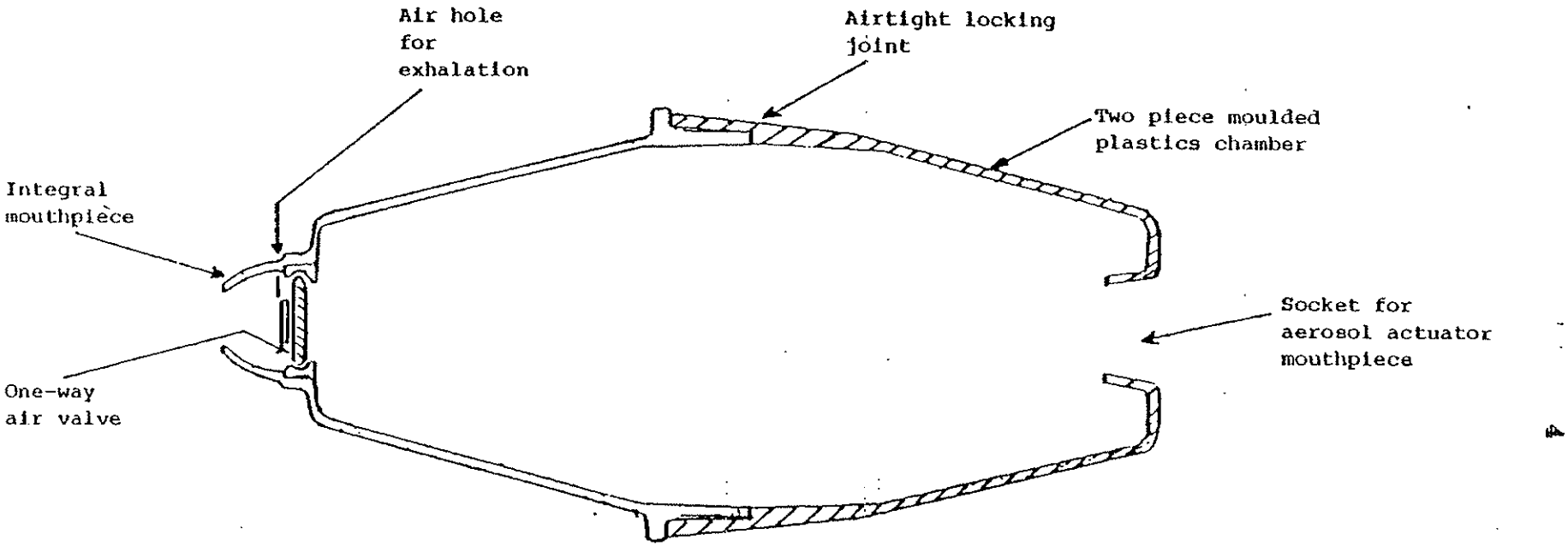


Figure 1 Centre-line sectional longitudinal view of the 750ml spacer.

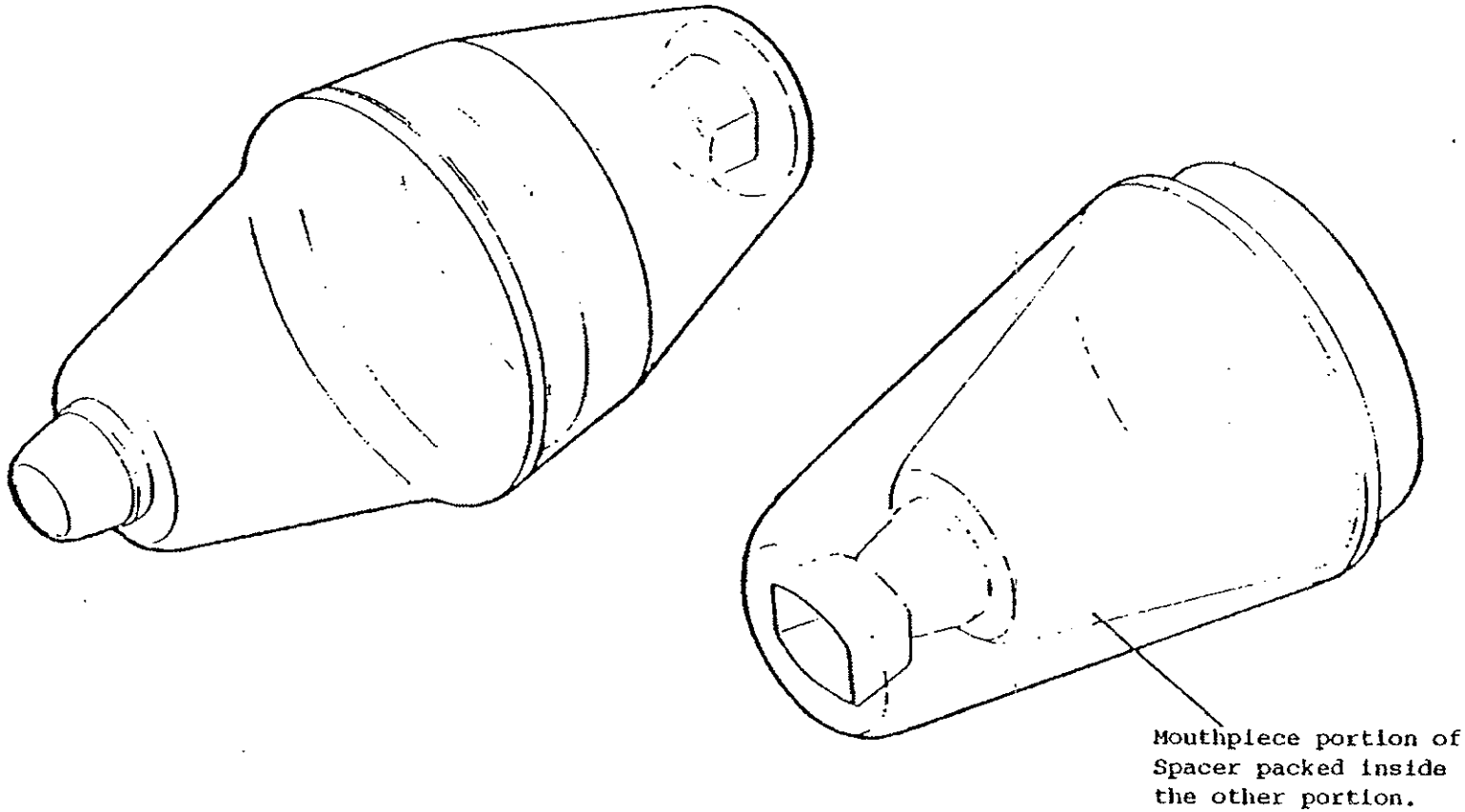
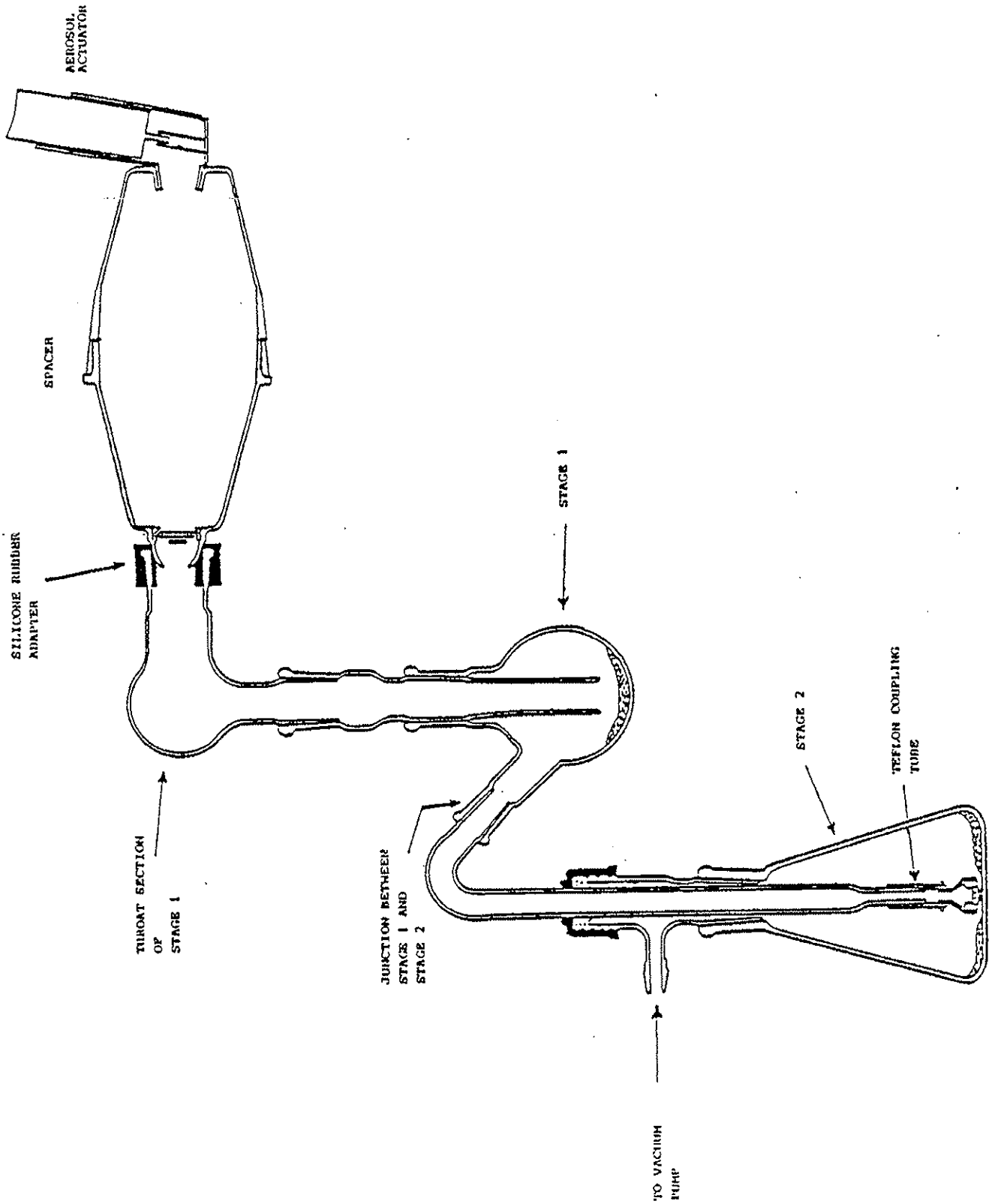


Figure 2. Exploded view of the 750ml spacer in the assembled and packed arrangements.


AEROSOL ACTUATOR
SPACER
SILICONE RUBBER ADAPTER
STAGE 1
THROAT SECTION OF STAGE 1
JUNCTION BETWEEN STAGE 1 AND STAGE 2
STAGE 2
TEFLON COUPLING TUBE
TO VACUUM PUMP

e) The dried can was reweighed.

f) A similar procedure to steps a - e was applied to spacer number 10 only, using cans a - j in turn and firing shots 23-32 from each can.

3.2.2. Evaluation of the effect of accumulating multiple shots in the spacer before withdrawal of aerosol.

For this experiment 3 further aerosol cans were used, designated k - m. They were each fired into spacer number 10, but in this case 3 ranges of shots 13 - 22, 23 - 32 and 33 - 42) were each studied on each can/spacer combination using a different procedure. In all cases, each can was shaken for 30 seconds before firing each shot and a 2 second pause was observed after firing each shot before either switching on the vacuum pump or shaking the can, whichever was appropriate. For shots 13 - 22, a pair of shots was accumulated in the spacer before switching on the vacuum pump for 10 seconds only. This procedure was repeated until a total of 10 shots had been fired and collected. The deposited drug in the various components was then washed out and measured as before. For shots 23 - 32, a group of 5 shots was fired into the spacer before each withdrawal of aerosol, two groups (10 shots) being collected. For shots 33 - 42 a single group of 10 shots was accumulated in the spacer before withdrawal. These procedures were each applied to cans k, l and m on each of the two aerosol products.

3.3 Analysis Methods for Deposited Drug.

3.3.1 Sample Solutions

The drug fractions deposited in the actuator/spacer combination and in stages 1 and 2 of the Twin Impinger were each washed out with methanol into a separate 100ml volumetric flask. To each sample was added the appropriate volume of distilled water to match the concentration in the mobile phase of the appropriate product. All the flasks for both aerosol products were then made up to volume with methanol.

3.3.2 Standard Solution

These were prepared at concentrations within the ranges of 1.19 and 1.54µg ml^{-1} for beclomethasone dipropionate and 3.78 - 5.67µg ml^{-1} for salbutamol.

3.3.3 Materials

Methanol, hplc grade (Fisons)
Hexane, AR Grade (BDH)
Propan-2-ol, AR Grade (BDH)
Distilled water, double distilled in an all-glass still
Ammonium acetate, AR Grade (BDH).

3.3.4 Hplc Conditions

200µl volumes of each sample and of standard solution were injected manually via a 200µl Rheodyne loop valve on to the column using the following conditions:

Mobile phase: methanol-water (70:20) for beclomethasone dipropionate.

methanol-1.2 x 10^{-2}M aqueous ammonium acetate (75:25) for salbutamol.

Column: 150 x 5mm packed with Hypersil ODS 5µm reverse phase packing material. The packing material was slurried into propan -2-ol and packed using a CPIII Slurry Packer (Jones Chromatography) with hexane as packing solvent at about 3500 psi pressure. The conditioning solvent was propan-2-ol at about 3000 psi pressure.

Equipment: The hplc equipment consisted of a Constametric IIG pump (Laboratory Data Control) coupled to an LC-UV 3 variable wavelength detector (Pye-Unicam) and CR 6505 recorder (J.J. Instruments).

Flow Rate: 1.5ml min^{-1} (beclomethasone dipropionate).
2.0ml min^{-1} (salbutamol).

Detector: Wavelength set at 239nm (beclomethasone dipropionate).
276nm (salbutamol).

Temperature: Ambient.

Sensitivity: 0.04 - 0.08 A.U.F.S.D. (beclomethasone dipropionate).
0.02 A.U.F.S.D. (salbutamol).

3.3.5 Calculation of Results

Drug concentration was determined from duplicate injections of test sample (T) bracketed by duplicate injections of standard drug sample (S) according to the pattern,

$SST_1T_1T_2T_2SST_3T_3$.....

The results were calculated by the following method:

$$\text{Hplc sample conc. } (\mu g ml^{-1}) = \frac{\text{Mean peak height (mm) sample}}{\text{Mean peak height (mm) of standard}} \times \text{Standard conc } (\mu g\ ml^{-1})$$

The hplc sample concentration was calculated separately against each of the two individually prepared external standards. These two values were meaned and used to calculate the drug weight in the various deposition stages.

Drug weight = mean hplc sample conc. x volume of collection flask x dilution factor

4. RESULTS

4.1 Weight of Metered Dose of Beclomethasone Dipropionate and Salbutamol.

Tables 4.1 and 4.2 show the results for the total weight of beclomethasone dipropionate and salbutamol delivered from the metering valve of Becotide Inhalers and Ventolin Inhalers. Each result is for 10 doses, each one being withdrawn separately from the spacer into the Twin Impinger. The results are shown for:

a) 10 can (a - j) each fired into a separate spacer (1 - 10) and measured on shots 13 - 22 from each can.

b) For each can (a - j) fired from shots 23 - 32 into spacer number 10 only.

Each result is the total drug recovered in each case from the actuator/spacer and the two stages of the Twin Impinger. The results also include the mean single dose, standard deviation (SD) and coefficient of variation (CV).

The mean doses of each group are comparable to those normally found for Becotide Inhaler or Ventolin Inhaler respectively in the absence of a spacer and the individual results lie within the dose specification for these products.

4.2 Percentage Deposition of Beclomethasone Dipropionate and Salbutamol in the Actuator/Spacer and Stages 1 and 2 of the Twin Impinger.

The results show the percentage drug fractions deposited in the actuator/spacer combination and in stage 1 and stage 2 of the Twin Impinger, for Becotide Inhaler (Table 4.3) and Ventolin Inhaler (Table 4.4). The can/spacer combinations and ranges of doses examined correspond to those already described in Tables 4.1 and 4.2 for total metered dose. Each result is calculated as a percentage of the total drug recovered from the actuator/spacer and the two stages of the Twin Impinger (i.e. of the total metered dose).

The results show that the stage 2 fraction delivered by the spacer when collecting the aerosol in single dose at a time ranges from 40.5 - 54.3% for Becotide Inhaler and 38.1 - 54.9% for Ventolin Inhaler. Such data have previously been reported to the DHSS, as described in Section 3. These ranges are similar to those found for these two aerosol products in the Twin Impinger in the absence of a spacer. Using the spacer, stage 1 results for the Twin Impinger range from 2.0 - 6.4% for Becotide Inhaler and 2.7 - 11.9% for Ventolin Inhaler. These results are markedly lower than the range of about 30 - 40% which is normally found for both these inhalers in the Twin Impinger in the absence of a spacer. In contrast, the present results for the fraction retained in the actuator/spacer combination, about 40 - 45% of the metered dose for both aerosol products, are much higher than the usual results for both products which are higher than the usual results for both products which are generally about 10 - 20% in the actuator in the absence of a spacer.

The Twin Impinger stage 2 fraction consists of the finer aerosol particles of drug which can pass through the inlet throat and the stage 1 impinger stage of the Twin Impinger. Both these regions trap large particles, the throat catching high velocity large droplets and the upper impinger stage traps particles at a controlled airflow according to its calibrated cut-off behaviour. This has an effective (50%) cut-off size of 6.4μm (mass mean aerodynamic diameter, MMAD) with an absolute cut-off at 10μm.

It is apparent from the results that the spacer is effective in its expected role in that it essentially retains the aerosol fraction which would normally deposit in the patient's oropharyngeal region (stage 1) in the absence of a spacer and yet still delivers essentially the same fine particle aerosol fraction (stage 2).

4.3 The Effect of Accumulating Multiple Doses in the Spacer before withdrawal of Aerosol into the Twin Impinger.

The Results in Tables 4.5 and 4.6 show the effect of accumulating more than one shot in the spacer before applying vacuum to draw the aerosol cloud into the Twin Impinger. This is shown for Becotide Inhaler (Tables 4.5 and 4.7) and Ventolin Inhaler (Tables 4.6 and 4.8) on cans k, l and m of each product. In each case 5 groups of 2 doses (shots 13 - 22), 2 groups of 5 doses (shots 23 - 32) and one group of 10 doses (shots 33 - 42) were examined on each can, all in spacer number 10.

The results in Tables 4.5 and 4.6 show the metered dose weight of beclomethasone dipropionate and salbutamol respectively, as the total drug recovered from the actuator/spacer, and the 2 stages of the Twin Impinger. Clearly there is little effect on the metered dose of drug when firing by the three regimens, and the results are similar to those shown on Tables 4.1 and 4.2 where single doses at a time were collected in the spacer.

Table 4.1 Becotide Inhaler in the 750ml spacer
Weight of metered dose of beclomethasone dipropionate in 10 shots

Each result is the total drug in mcg recovered from the actuator/spacer and stages 1 and 2 of the Twin Impinger, single doses being collected in the spacer prior to withdrawal of aerosol.

Can Ref.	Spacer Ref.		Weight of beclomethasone dipropionate in 10 doses (mcg)	
	Shots 13 - 22	Shots 23 - 32	Shots 13 - 22	Shots 23 - 32
a	1	10	463	443
b	2	10	440	430
c	3	10	442	457
d	4	10	468	484
e	5	10	477	467
f	6	10	438	429
g	7	10	462	440
h	8	10	438	428
i	9	10	444	442
j	10	10	454	466
Mean single dose (mcg)			45.26	44.86
S.D.			1.42	1.91
C.V. (%)			3.13	4.25

Table 4.2 Ventolin Inhaler in the 750ml spacer
Weight of metered dose of salbutamol in 10 shots

Each result is the total drug in mcg recovered from the actuator/ spacer and stages 1 and 2 of the Twin Impinger, single doses being collected in the spacer prior to withdrawal of aerosol.

Can Ref.	Spacer Ref.		Weight of salbutamol in 10 doses (mcg)	
	Shots 13 - 22	Shots 23 - 32	Shots 13 - 22	Shots 23 - 32
a	1	10	946	907
b	2	10	906	1002
c	3	10	849	780
d	4	10	859	866
e	5	10	942	932
f	6	10	933	917
g	7	10	948	1179
h	8	10	1084	1066
i	9	10	1117	959
j	10	10	1022	992
Mean single dose (mcg)			97.30	98.00
S.D.			8.43	9.53
C.V. (%)			8.66	9.72

Table 4.3 Becotide Inhaler in the 750ml spacer
Percentage deposition of beclomethasone dipropionate in the actuator/spacer and stages 1 & 2 of the Twin Impinger.

Each result is measured on 10 metered shots of Becotide Inhaler, and is calculated as a percentage of the total deposition in the actuator/spacer and the Twin Impinger.

Can Ref.	Spacer Ref. Shots 13-22	Spacer Ref. Shots 23-32	Actuator and Spacer Shot Numbers 13-22	Actuator and Spacer Shot Numbers 23-32	Stage 1 Shot Numbers 13-22	Stage 1 Shot Numbers 23-32	Stage 2 Shot Numbers 13-22	Stage 2 Shot Numbers 23-32
a	1	10	48.8	47.4	5.6	2.0	45.6	50.6
b	2	10	52.5	46.5	3.6	4.6	43.9	48.9
c	3	10	51.5	44.9	2.9	4.2	46.0	50.9
d	4	10	45.7	43.6	3.4	4.5	50.9	51.9
e	5	10	51.8	49.7	3.8	2.8	44.4	47.5
f	6	10	52.1	42.0	3.2	3.7	44.7	54.3
g	7	10	56.9	42.9	2.6	6.4	40.5	50.7
h	8	10	50.5	46.5	3.2	6.3	46.3	47.2
i	9	10	48.0	44.6	3.8	4.1	48.2	51.3
j	10	10	42.7	45.5	3.7	6.3	53.6	50.2

Table 4.4 Ventolin Inhaler in the 750ml spacer
Percentage deposition of salbutamol in the actuator/spacer and stages 1 & 2 of the Twin Impinger.

Each result is measured on 10 metered shots of Ventolin Inhaler, and is calculated as a percentage of the total deposition in the actuator/spacer and the Twin Impinger.

Can Ref.	Spacer Ref. Shots 13-22	Spacer Ref. Shots 23-32	Actuator and Spacer Shot Numbers 13-22	Actuator and Spacer Shot Numbers 23-32	Stage 1 Shot Numbers 13-22	Stage 1 Shot Numbers 23-32	Stage 2 Shot Numbers 13-22	Stage 2 Shot Numbers 23-32
a	1	10	53.9	54.9	4.4	6.1	42.3	54.9
b	2	10	57.2	47.9	4.7	5.1	38.1	47.9
c	3	10	55.1	50.5	6.4	11.9	38.5	50.5
d	4	10	53.4	51.8	5.8	5.7	40.7	51.8
e	5	10	46.0	49.6	4.9	5.8	49.2	44.6
f	6	10	50.6	48.0	2.7	3.8	46.7	48.2
g	7	10	52.3	41.6	3.1	3.7	44.6	54.6
h	8	10	44.3	39.6	4.1	5.6	51.7	54.8
i	9	10	46.2	49.0	3.6	5.3	50.2	45.7
j	10	10	48.8	48.3	5.3	7.3	45.9	44.4

Table 4.5 Becotide Inhaler in the 750ml spacer
(multiple doses accumulated in the spacer prior to withdrawal of aerosol)

Weight of metered dose of beclomethasone dipropionate in 10 shots.

Each result is the total drug in mcg recovered from the actuator/ spacer and stages 1 and 2 of the Twin Impinger.

Shot Numbers		
13 - 22[a]	23 - 32[b]	33 - 42[c]
428	443	455
434	408	443
423	424	434

(a) 5 x 2 shots accumulated in spacer prior to withdrawal of aerosol

(b) 2 x 5 shots accumulated in spacer prior to withdrawal of aerosol

(c) 1 x 10 shots accumulated in spacer prior to withdrawal of aerosol

Table 4.6 Ventolin Inhaler in the 750ml spacer
(multiple doses accumulated in the spacer prior to withdrawal of aerosol)

Weight of metered dose of salbutamol in 10 shots.

Each result is the total drug in mcg recovered from the actuator/ spacer and stages 1 and 2 of the Twin Impinger.

Shot Numbers		
13 - 22[a]	23 - 32[b]	33 - 42[c]
1012	881	977
921	1068	1049
968	1075	1049

(a) 5 x 2 shots accumulated in spacer prior to withdrawal of aerosol

(b) 2 x 5 shots accumulated in spacer prior to withdrawal of aerosol

(c) 1 x 10 shots accumulated in spacer prior to withdrawal of aerosol

Table 4.7 Becotide Inhaler in the 750ml spacer
(multiple doses accumulated in the spacer prior to withdrawal of aerosol)

Percentage deposition of beclomethasone dipropionate in the actuator/spacer and stages 1 and 2 of the Twin Impinger

Each result is measured on 10 metered shots of Becotide Inhaler, and is calculated as a percentage of the total deposition in the actuator/spacer and the Twin Impinger.

Can Ref.	Actuator & Spacer			Stage 1			Stage 2		
	Shot Numbers			Shot Numbers			Shot Numbers		
	13 - 22 (a)	23 - 32 (b)	33 - 42 (c)	13 - 22 (a)	23 - 32 (b)	33 - 42 (c)	13 - 22 (a)	23 - 32 (b)	33 - 42 (c
k	44.2	51.0	77.6	5.6	4.3	2.0	50.2	44.7	20.4
l	44.5	53.7	61.6	3.0	4.2	2.1	52.5	42.1	36.3
m	45.4	54.5	62.4	4.3	4.5	4.4	50.3	41.0	33.2

(a) 5 x 2 shots accumulated in spacer prior to withdrawal of aerosol

(b) 2 x 5 shots accumulated in spacer prior to withdrawal of aerosol

(c) 1 x 10 shots accumulated in spacer prior to withdrawal of aerosol

Table 4.8 Ventolin Inhaler in the 750ml spacer
(multiple doses accumulated in the spacer prior to withdrawal of aerosol)

Percentage deposition of salbutamol in the actuator/spacer and stages 1 and 2 of the Twin Impinger

Each result is measured on 10 metered shots of Ventolin Inhaler, and is calculated as a percentage of the total deposition in the actuator/spacer and the Twin Impinger.

Can Ref.	Actuator & Spacer			Stage 1			Stage 2		
	Shot Numbers			Shot Numbers			Shot Numbers		
	13 - 22 [a]	23 - 32 [b]	33 - 42 [c]	13 - 22 [a]	23 - 32 [b]	33 - 42 [c]	13 - 22 [a]	23 - 32 [b]	33 - 42 [c]
k	54.7	62.7	77.5	8.7	7.4	7.1	36.6	30.0	15.5
l	49.4	74.8	82.6	10.1	8.1	5.3	40.5	17.1	12.0
m	54.3	72.1	75.2	9.4	5.8	5.6	36.3	22.1	19.2

(a) 5 x 2 shots accumulated in spacer prior to withdrawal of aerosol

(b) 2 x 5 shots accumulated in spacer prior to withdrawal of aerosol

(c) 1 x 10 shots accumulated in spacer prior to withdrawal of aerosol

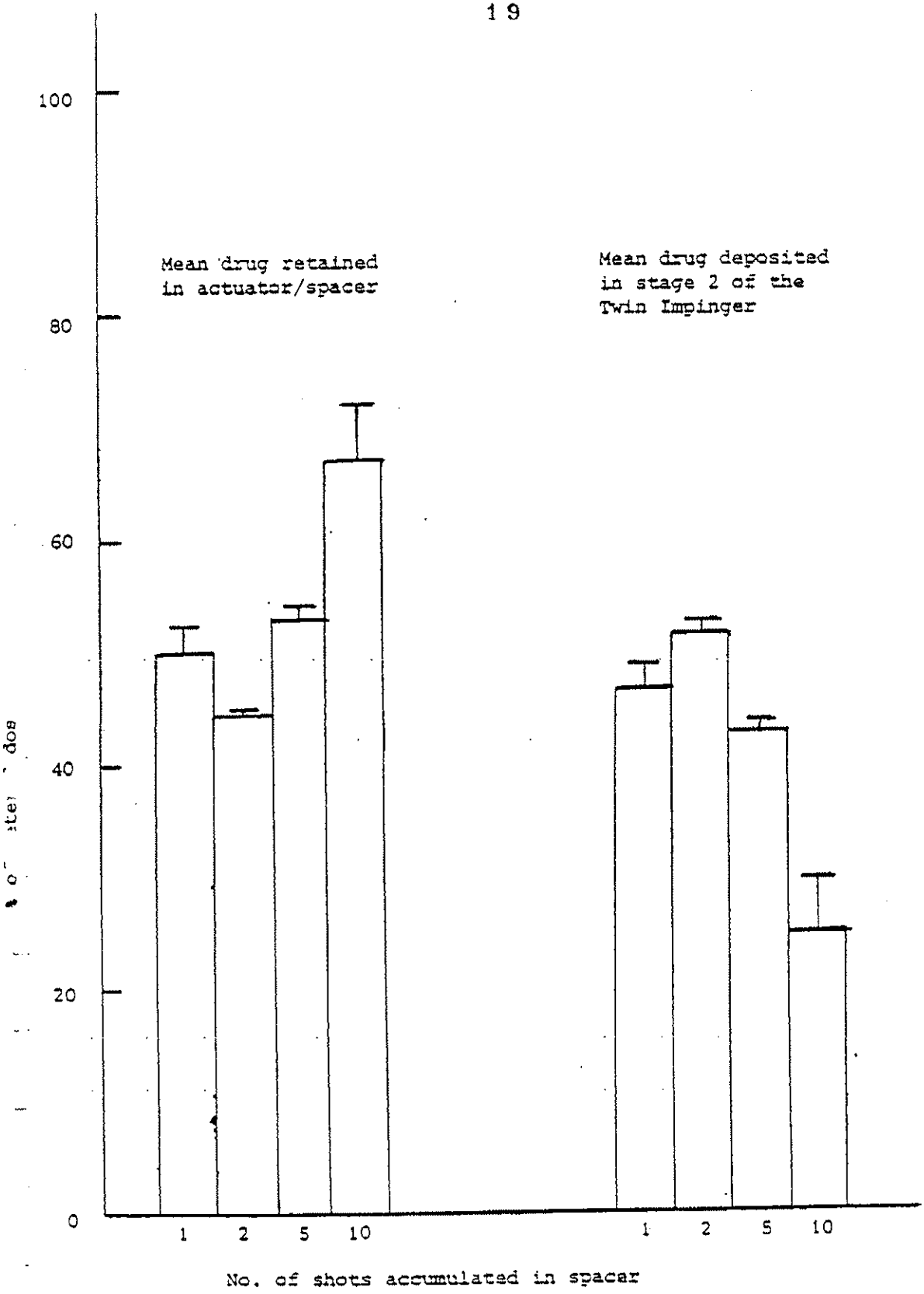


Figure 4.1 Becotide Inhaler fired through a 750ml spacer into a Twin Impinger - the effect of accumulating various numbers of shots in the spacer before withdrawal of aerosol.
(bar lines are the standard error)

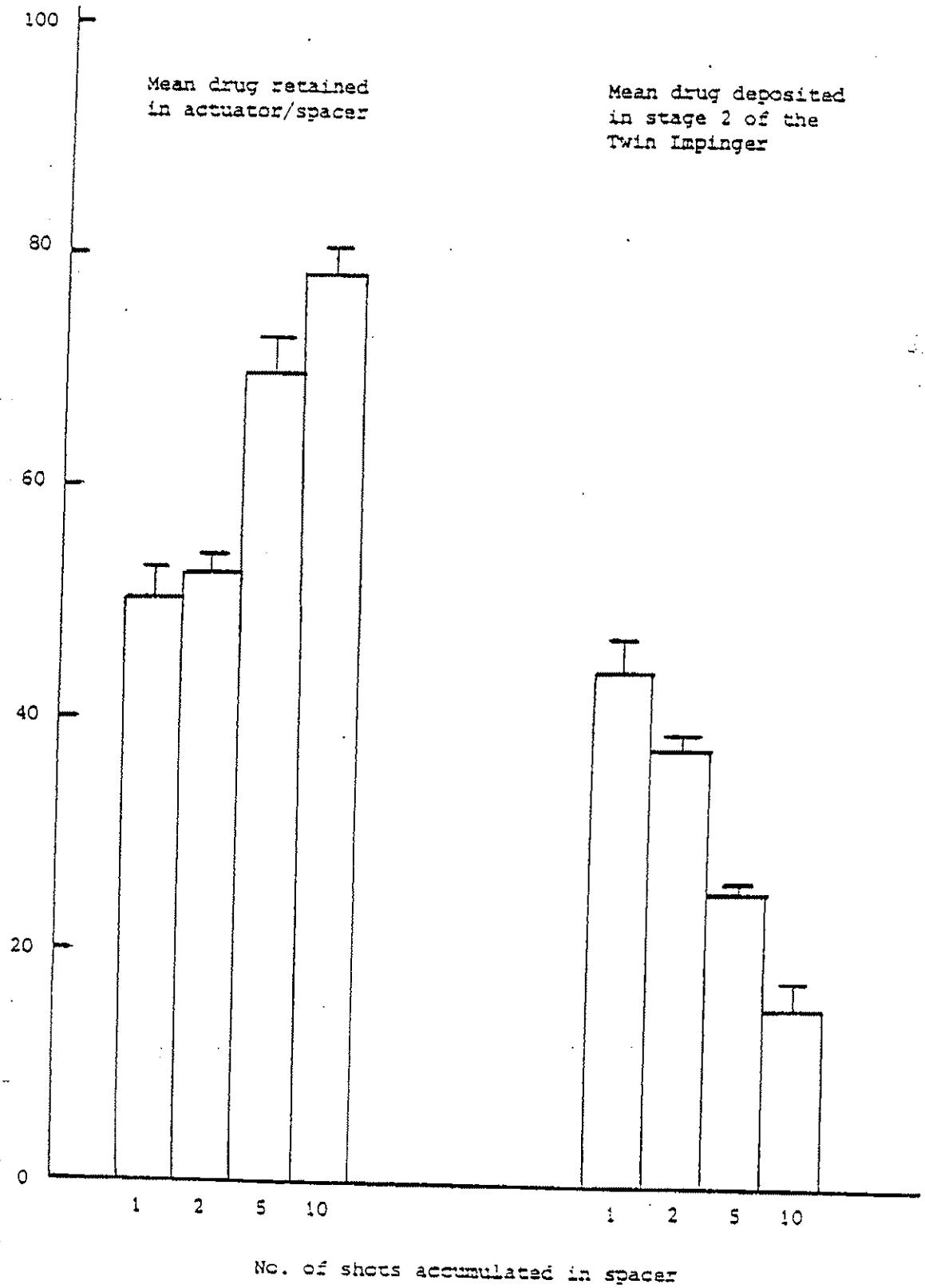


Figure 4.2 Ventolin Inhaler fired through a 750ml spacer into a Twin Impinger - the effect of accumulating various numbers of shots in the spacer before withdrawal of aerosol.
(bar lines are the standard error)

The results in Tables 4.7 and 4.8 show the corresponding Twin Impinger results as percentage fractions in the actuator/spacer and the two stages of the Twin Impinger. The stage 1 results are unaffected by the different regimes of firing the aerosol, but clearly there is an effect on the other two fractions. As the number of doses accumulated in the spacer prior to withdrawal is increased, there is a trend of increasing deposition in the actuator/spacer and correspondingly less in stage 2. This effect is much more marked with Ventolin Inhaler than with Becotide Inhaler. The changes can be seen quite strikingly in Figures 4.1 and 4.2 which show the percentage fractions in histogram form for the two product.

The results can be explained on the basis of increasing deposition of fine aerosol particles in the spacer due to wall losses caused by sedimentation and other factors when aerosol is held in the spacer for an increased time whilst further aerosol shots are fired into the spacer. The more profound loss with Ventolin Inhaler is probably related to its electrostatic particle charge characteristics. The results suggest that the loss of useful aerosol available to the lungs is likely to be significant after the accumulation in the spacer of 2 doses of Ventolin Inhaler or 5 doses of Becotide Inhaler. Naturally, greater losses would be expected if larger numbers of doses are accumulated in a similar manner.

4.4 Flow Behaviour of the Spacer Valve and Exhalation Hole

The flow resistance of the spacer one-way air valve in the open (inhalation) position was shown to be very low by passing air through the valve and the mouthpiece from the chamber side, with the exhalation holes sealed. The pressure drop was only about 2.5cm of water at an airflow of 60 litres min^{-1}.

The sealing ability of the valve, which should prevent exhalation air passing in to the spacer chamber, was measured by passing air to the spacer mouthpiece and covering the two exhalation holes. The pressure held in the mouthpiece was at least 20cm of water at a low air flow of 10 litres min^{-1} demonstrating good sealing.

The ease of airflow through the two exhalation holes was assessed by passing air through the valve and exhalation holes from the chamber, the mouthpiece orifice being sealed. The low resistance to flow was shown by the low pressure drop (2cm water at 20 litres min^{-1} and 10cm water at 50 litres min^{-1}).

These results demonstrate that the air valve has an effective seal on closing and a low resistance to inhalation flow. The valve opened from the closed position at a very low airflow passed into the chamber of about 5 litres min^{-1}. The exhalation holes allow easy passage of air during exhalation. These results were verified by sucking and blowing at the spacer mouthpiece, which readily demonstrated subjectively the correct operation of the valve and exhalation holes.

5. CONCLUSIONS

The results of this study show that the amount of aerosolised drug delivered from Becotide Inhaler and Ventolin Inhaler through the new spacer to stage 2 of the Twin Impinger was similar to that delivered from the aerosol products when used without a spacer. This applied when single doses are fired into the spacer and then withdrawn after a pause of two seconds. This should aid the coordination of certain patients who have difficulty in correctly synchronising the firing of metered dose inhalers and inspiration, as the patient can exhale through the spacer mouthpiece and then inhale within a second or two.

The oropharyngeal deposition of drug is expected to be reduced to about one eighth of that found without a spacer, on the basis of the marked reduction in stage 1 deposition in the Twin Impinger. The reproducibility of drug delivery from the spacer to both stage 1 and stage 2 of the Twin Impinger is satisfactory amongst a group of ten prototype moulded spacer.

There was a trend of decreasing Twin Impinger stage 2 results when increasing number of aerosol shots were accumulated in the spacer before withdrawal of the aerosol cloud, particularly with Ventolin Inhaler. These results suggest that it would be preferable to fire one or two shots at a time before inhalation and to repeat this procedure for the required number of times if high lung dosage is required.

The spacer air valve has satisfactory sealing ability and low flow resitance when open and should enable satisfactory alternate exhalation of the by-pass air and inhalation of aerosol through the spacer chamber.

The results do not demonstrate any significant increase in stage 2 deposition from either aerosol product which can be ascribed to the use of the spacer. However, it is possible that detailed studies with a cascade impactor would demonstrate some increase in the very fine particle fraction delivered from a spacer. Any such difference would probably be extremely difficult to demonstrate clinically in view of the masking effect of improved coordination with a spacer in some patients.

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TM/PTS/98/0035 **CONFIDENTIAL - NOT TO BE COPIED**

To: Anne Alvers ✓

Author : Michael Symington

Function:	Respiratory Technology Cell
Site:	Speke
T.M. Number:	**TM/PTS/98/0035**
Confidentiality:	Confidential
Title :	Comparison of Volumatic™ Inhalation Spacer Devices of different ages.

No. of pages : 4 + 1 Appendix Copy No. : 4

TECHNICAL MEMORANDUM

Distribution:
Master Document with B Gibson - Quality Systems, Speke

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25-Sept-03

Approved by: S.E. Southerden Date of Issue 29th January 1998.

GLAXO WELLCOME

Introduction

This technical memorandum details the comparison of several Glaxo-Wellcome Volumatic™ inhalation spacer devices. The work was undertaken in order to show equivalent performance of devices of different ages.

Method Details

The experimental work was performed using the HPLC conditions specified in the method supplied by Jo Ellis, analyst in NPI&PT, Glaxo Operations, Ware - See Appendix 1. Standards were prepared to give a concentration equivalent to that detailed in the method.

Following advice given by analysts at GWRD, Ware, care was taken to prevent static charge build up on the Volumatics. This was necessary because static charge rapidly attracts drug particles from the aerosol cloud and leads to increased deposition in the spacer device. These precautionary steps included an initial rinse with Methanol, followed by a water wash. The device was then left to air dry. During insertion of the Volumatic into the special low-conductive mouthpiece, a damp paper towel was used to handle the volumatic. Extra care was taken not to handle the device with fingertips at any stage. After assembly, the Spacer device was wiped with a wet paper towel and allowed to dry, using an anti-static fan to assist. The fan was left on continuously through the firing of actuations into the apparatus.

The regime for firing was as follows:

The inhaler was shaken for approximately 30 seconds. Two actuations were then fired into the volumatic with a few seconds in between each actuation. The twin impinger pump was then turned on for 3 seconds and turned back off. This regime was repeated until a total of 10 actuations had been delivered into the volumatic.

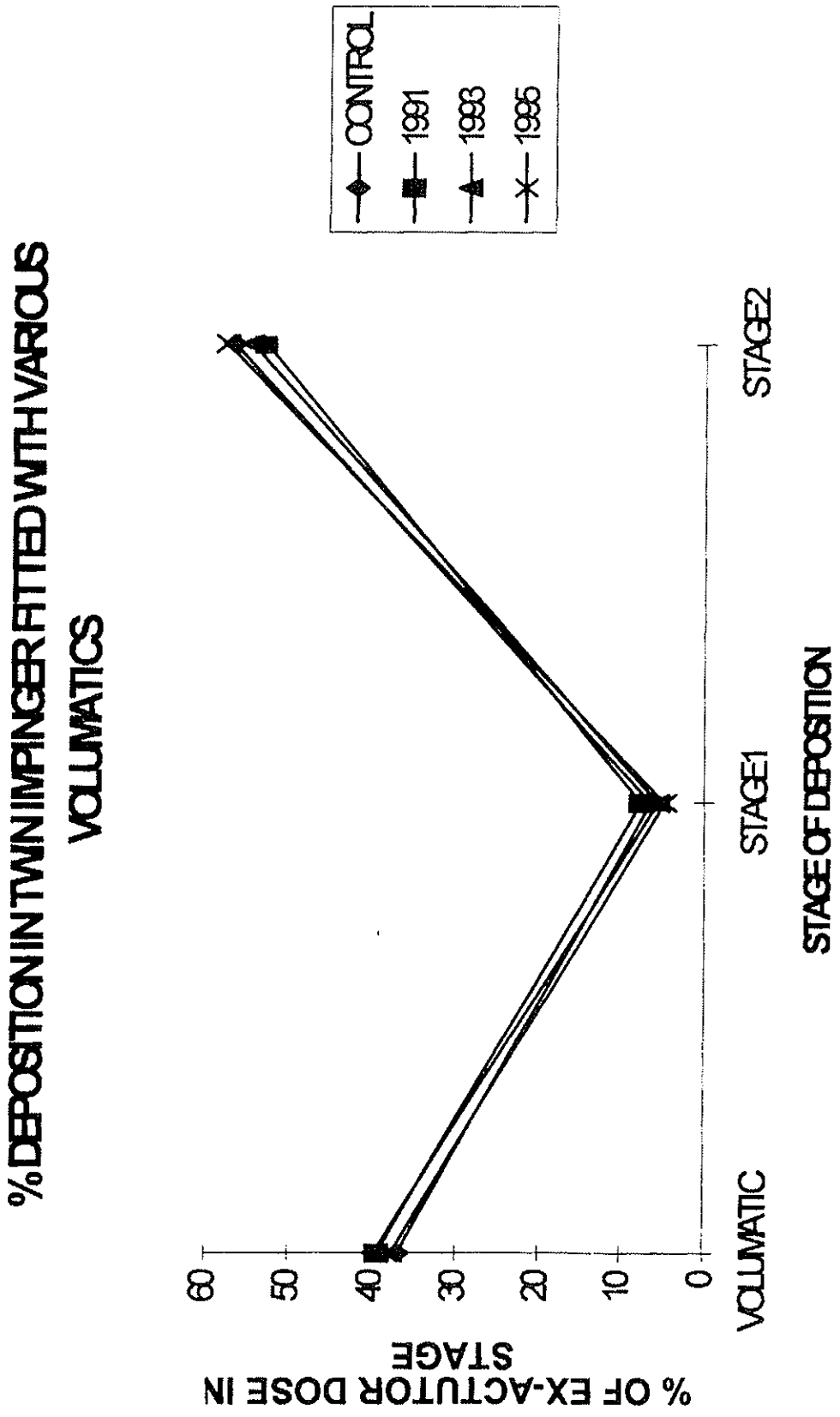
Deposition was assessed in the volumatic itself, in stage 1 (including the mouthpiece), and stage 2. The valve and actuator deposition was not assessed because this was not considered relevant to comparison of the performance of the volumatics.

Batch Details

Ventolin (P11/P12) Metered Dose Inhaler, 100µg ex-valve; 200 actuations.
Batch No 10339193. Manufactured 30/09/97

Results

Age of Volumatic	Volumatic (µg) (% of ex-act dose)	Stage 1 (µg) (% of ex-act dose)	Stage 2 (µg) (% of ex-act dose)
control (1997) (L0110 0293)	30.4 **(36.9%)**	5.3 **(6.4%)**	46.8 **(56.8%)**
1991 (S0024543)	41.2 **(39.4%)**	7.8 **(7.5%)**	55.4 **(53.0%)**
1993 (G0040668M)	33.3 **(39.8%)**	4.6 **(5.5%)**	45.7 **(54.7%)**
1995 (G0111780 J)	33.4 **(37.7%)**	4.1 **(4.7%)**	51.1 **(57.7%)**


% DEPOSITION IN TWIN IMPINGER FITTED WITH VARIOUS VOLUMATICS
CONTROL
1991
1993
1995
% OF EX-ACTUTOR DOSE IN STAGE
60
50
40
30
20
10
0
VOLUMATIC
STAGE1
STAGE2
STAGE OF DEPOSITION

Conclusions

This investigation reveals equivalent performance of all the volumatics examined and confirms that when handled correctly the Volumatic is an effective spacer device.

Author..... Date..28 Jan 98.....

J2956 Volumatic mouthpiece 21 Jan 97

Purpose To assess TIMP Sr. 2 deposition using new volumatics vs Control. (ie Non-modified mouthpiece).

Method: V9014 - Salbutamol only.

System 3
Ref: PTO 248.047

Standards
Ref PTO 248.047 - 048

Mobile phase
Ref PTO 248.047 for Buffer.

- 3.5 l MeOH + 1.0 l H_2O + 10.0 ml buffer.
Prep 21 Jan 97 exp 28 Jan 97

Sample prep: Can Batch WA40A 449.

6 cans used - see P. 052 Can nos 3 → 8 used. Further priming not necessary, using final shots wts as initial wts. P.58

Twin Impinger apparatus was set up with air flow at 60 l/min, then the volumatic was supported with a clamp and the ~~mouth~~ JE 23.1.97 mouth part placed into a special rubber mouthpiece. Before testing, the volumatics were washed with methanol and allowed to dry, then washed with distilled water and allowed to dry overnight.

Before firing the dosed the volumatic was wiped gently with a damp paper towel until the static readings from the device were zero. (Note borrowed from M. Blanchard

Signature: JE Checked By: V. Lawrence
23 Jan 97 23rd Jan 97

Appendix 1

DS 5

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14th January 97

PTD 248 048

Seevent 120 dose Actuators — Twin Impingers — J.No. 2954

cont. from PTD 248/047

Standards - cont.

Batch no.	J.N. 2954	
14.01.97	13:29:51	
1 STD 1	66.21 mg	
2 STD 2	66.31 mg	

PTD 248/048
V Lawman
15th Jan 97

Std → 100.0 ml methanol = S1 ✓ prep: 14th Jan 97 exp: ~~14th~~ 26th Jan 97 ✓ VL 15.1.97

10.0 ml (S1) → 100.0 ml methanol = S2

5.0 ml (S2) → 30 ml d/water → 100.0 ml with methanol = RF Soln.

RF soln + S2 diluted from (S1) fresh daily. ✓

Sample Preparation

Can Batch No. WA40A0449 ✓ Ventolin 11/12 200 actuations 100 µg

Batch No. removed from can + 3d no. scratched on. Apparatus assembled ✓ 15.1.97 as per method with 30ml methanol in stage 2 + 7ml methanol in stage 1. Canister primed by shaking can for 30secs then firing 1 shot, waiting 5 secs then firing 2nd shot (to waste). Actuator + valve stem cleaned with methanol and allowed to dry. Can weighed, then placed in actuator. Pump set at 60L/min. Can shaken for 30 secs then 1 shot fired into twin impinger apparatus, inhaler shaken for 5secs then 2nd shot fired into twin impinger, this was repeated until 10 shots had been fired.

Valve + actuator washed with methanol into a 25.0ml flask containing 7.5ml d/water.

Stages 1+2 each washed with methanol into 100.0 ml flasks containing 30ml d/water when ambient made up to volume with methanol.

Actuator Cavity No's 53 → 60 inc.

Signature: V. Lawman ..... Checked By: .....

Appendix 1

DS 4

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TOTAL P.03

PTD 248 047

Seasevent 120 dose Actuators Trial Analyses Jan 2554

Purpose: To test deposition of actuators after tooling modification. Salbutamol cans were supplied for testing (as this is just an analysis to confirm that the actuators perform correctly and that stage 2 % is correct) this was not critical. Also method states uses a 20cm 5um Spheriosorb columns, a 25cm column was used as these were not easy 20cm columns available, this does not invalidate the method.

Method: V90/4 - salbutamol only.

System 3

Columns: 25cm x 4.6mm 5um Spheriosorb ODS1. INH Stn. 117

Oven Temp. 40°C

Flow rate: 2.0ml/min.

Detector: 270 nm

Injection vol: 200ul.

Mobile Phase:

6.75% Ammonium Acetate Soln.

Bal. M4384 S.V 2954

14.01.97 10:47:04

20 Ammon. Acetate 6.7494 g → 100.0ml dI water, prep: 14th Jan 97, exp: 14th Feb 97

PRO24S/con7 V Hammam 14th Jan 97

3.5% methanol + 1.0% dI water + 10.0ml buffer prep: 14th Jan 97. exp: 21st Jan 97

Standards

Salbutamol Base, Alfa 21F, Vial no. 258139, Purity 95.2%, use by: 26th Jan 97

Signature: V. Hammam Checked By: JDL

22 Jan 97

04-DEC-1997 14:48 FROM GLAXO OPERATION ITU TO 79254289 P.03

DS7.

J2956 Volumatic spacers 23 Jan 97

Gwen Building 5).

The can was shaken 30 secs. + 2 actuations fired into the device. After 2 seconds the pump was switched on for 3 seconds using a timer. This was repeated 4 more times, firing a total of 10 actuations into the apparatus.

The V+A JE 23.1.97 cord was washed out into a 250ml vol. flask containing 7.5 ml H2O using MeOH.

The Volumatic, ST1, and ST2 were each washed separately into 100.0 vol flasks containing 80ml H2O using MeOH.

Initial WT		Final WT.	Shot wt	
26.1965	3	25.3354 g	86.11	86 ✓
26.2618	4	25.4054 g	85.64	86 ✓
26.2066	5	25.3481 g	85.85	86 ✓
26.2409	6	25.3796 g	86.13	86 ✓
26.1466	7	25.3006 g	84.60	85 ✓
26.3173	8	25.4725 g	87.48	87 ✓

SN 19324 J2956 JE 22.01.97 Pro24.05 09:13:01

Column Check

Start Sabmdi 010.001 End 011.076

Plates	7090	6562	Transcription Checked A.Wilson 23rd
Tailing	1.71	1.88	

Signature: JE 23.1.97

Checked By: V. Lawrence

Date: 23rd January 97