James Walker

Extractables & leachables - A converter's view

A technical paper
Presented by
James Walker & Co Ltd
(First presented at the RAPRA conference, London, September 2010)

High Performance Sealing Technology

EXTRACTABLES & LEACHABLES – A CONVERTER'S VIEW

Presented at the RAPRA conference
"Extractables and Leachables for Pharmaceutical Products 2010"
September 14-15 201, London, UK
This paper is reproduced with kind permission of ismithers (www.ismithers.net)

ABSTRACT

The need for cleanliness and biocompatibility is paramount for the Bioprocessing industries. An increased focus on the potential risk of leachables in recent times has increased the pressure on polymer converters to go to extreme lengths to minimise leachables from their products. How this can be achieved in mixing elastomeric materials for BioPharmaceutical sealing applications is discussed. This is extended to downstream processing such as moulding and subsequent finishing and handling of elastomeric components. A brief review of the current test requirements, and test methods employed, is given and how this is achieved through careful operational practices in both mixing of the elastomeric material, and subsequent processing, supported by data gathered in manufacture.

INTRODUCTION

Seals are used throughout the BioPharmaceutical and Pharmaceutical industries, their uses are primarily in hygienic clamp fittings, diaphragm valves, and o-rings.

Their function is integral to process performance. They maintain the integrity of the process, and isolate the process from the outside conditions, so not to allow leaks and or contamination. The issue of extractables and leachables in Bioprocessing has received increased attention in recent years, particularly with advent of single use technology and the consequent increased use of polymeric materials. James Walker and Co. Ltd. have developed a range of materials, and products, specifically for sealing of Bioprocessing equipment that take into consideration current requirements on extractables and leachables, as well as other performance criteria.

This paper outlines the compounding, manufacturing, and operational aspects required to ensure minimal extractables and leachables.

DEFINITION OF EXTRACTABLES AND LEACHABLES

There are numerous definitions of extractables and leachables, for the purpose of this paper these are defined as is proposed for the ASME BPE Standard 2012, which is;

> Extractables are chemicals that can be removed from final articles using appropriate solvents (eg. polar and non-polar) for the purpose of identification and quantification of potential leachables.
>
> Leachables are chemicals that migrate from the final article into the process fluid of interest (eg. water, buffered solutions, drug product, etc.) under normal and/or accelerated conditions (typically exposure time and/or temperature). Leachables are typically a subset of extractables, but can also be created as a result of chemical reactions with other leachables and/or components.

BASIC RUBBER COMPOUND

Rubber compounds are a complex, reactive mixture and typically contain numerous ingredients including the base polymer, carbon black, mineral fillers, plasticisers, processing aids, curatives, antioxidants, heat stabilisers, etc.

However, in an effort to meet the demands of the extractable testing a material has to be developed to give minimal risk of leachables, yet still maintain the other performance criteria expected from such seals (see below), as well as being processable. Naturally, a clean compound will be dependant on the cleanliness of the ingredients employed. Therefore, to address the issue of extractables specifically, we must start with the raw ingredients of the compound. A good place to start is to ensure that the

ingredients are on the FDA 21 CFR 177.2600 positive list, and avoid any ingredients that are known to be cytotoxic, having already screened several common ingredients for this.

Each of the ingredients present in elastomeric compounds for this industry should be carefully selected to ensure performance both mechanically and from a cleanliness viewpoint, processability (mixing, extrusion and moulding) as well as consistency of supply and traceability. Each of the ingredients is supplied with a Certificate of Analysis giving confidence in a consistent product. Such Certificates of Analysis are stored on record indefinitely for each batch received should they be required for future investigations and audits under the GMP regime.
It is also necessary to ensure that if pre-dispersed materials, in polymer or oil, are used that the carrier does not cause a problem either. It is preferred to use “pure” materials, without a carrier, with minimal contaminants; reference to the C of A and specification is important here. Consideration must also be given to any possible by-products of each ingredient, as well as any potential synergy between two or more additives that may lead to toxicity problems.

An additional requirement of the materials that make up the final compound is that they must be free from animal derived ingredients (ADIF). This is more complex than it may first appear; as many raw material suppliers inadvertently use animal derived products in the manufacture of their products. As an example, some polymer manufactures and additive suppliers, use stearates, and waxes in their own processing, many of which are animal derived. Therefore, to ensure the ADIF criteria is satisfied, a clear understanding of the supplier processes and materials is essential.

This approach has been adopted for all materials intended for biopharmaceutical applications, and is embraced in the James Walker Elast-O-Pure range of materials, which includes EPDM, FKM and silicone in the range. For the purposes of this paper, only the EPDM compound, Elast-O-Pure EP 75B, is discussed

COMPOUNDING

Prior to mixing a thorough review of, and investigation, of the process flow was carried out. This was then followed by Failure Mode Effect Analysis (FMEA), to identify any potential critical steps with respect to cleanliness, resulting in a Process Control Plan, which was then implemented. Additionally, several go/no go systems have been employed, to minimise potential error sources. For example, use of balances that will not allow the process to proceed if the ingredient weight is outside +/- 2% limits.
On computer controlled mixing, the weight and batch of each individual ingredient is recorded and automatically filed for any required future reference, and to give full traceability of each component in each mix. This is supported by a manual record. Additionally, each material is used specifically for Bioprocessing products, avoiding possible cross contamination with materials mixed, possibly containing non-bioprocessing additives. At the weighing stage dedicated tooling is employed, again specific to bioprocessing material mixes, to eliminate any possible cross contamination.
As the mixing plant is used for numerous materials for different applications, it is essential to have a rigorous clean down procedure before mixing these materials. This consists of a thorough clean down of all work surfaces, prior to any operation being carried out. Additionally, the production of a range of materials is scheduled such that the mixing unit is as clean as possible as the mixing of materials for bioprocessing applications is approached. Prior to mixing the mixing unit is cleaned out using a full shot of a special cleaning compound designed to pull out any residual material from the mixer. is put through the mixing plant, effectively removing any residual material from previous mixes. Scheduling comes back into play again, as the first batch of the bioprocessing material mixed is quarantined, and shelved off for less critical, non-bioprocessing applications. In this way, any possible contamination of the material to be used in bioprocessing components is the material itself ! In addition, multiple batches of material are mixed consecutively, again to minimise any possible cross contamination.

Once mixed the material is dumped onto a recently cleaned two roll mill, milled and sheeted off. After cooling in air, without the use of anti-tack agents, it is then wrapped and sealed in polyethylene sheeting, also ADIF and free from plasticisers etc. before quarantining where it remains until batch testing is completed.

Every possible precaution has been taken at the mixing and compounding stage to minimise the possibility of contamination, and the level of extractables, ensuring complete traceability, whilst maintaining suitable mechanical properties to effect and maintain a seal.

TEST METHODS

Before releasing the material to production each batch must undergo additional qualification testing, over and above that for used for materials for non-bioprocessing applications. An internal specification has been drafted, bearing in mind the needs of the industry and is shown in JW 200 192. Standard rheological measurement is also determined to assure good processability.
The identified limits are either set by the indicated standard or by historical records on measurements on Elast-O-Pure EP 75B, an EPDM material specifically formulated for the bioprocessing industry.

The mechanical testing is recorded to ensure not only good uniform mixing of the material, and the material is to standard and suitable for use as a seal material. Note also that an internationally recognised extraction test, FDA 21 CFR 177.2600 is also carried out on each mixed run. This serves two purposes; firstly to ensure a clean mixing process is carried out and secondly, it is used as a quality control method.

A more detailed analysis of the extractable data, from the mixed compound, according to FDA CFR 177.2600 (limits : 20 mg/sq.in after 7 hours; 1 mg/sq.in after 7 + 2 hours) is shown in Figure 1 below for each Elasto-O-Pure EP75B batch, for the initial 7 hour extraction, and in Figure 2 for the secondary 2 hour extraction using a soxhlet extraction.

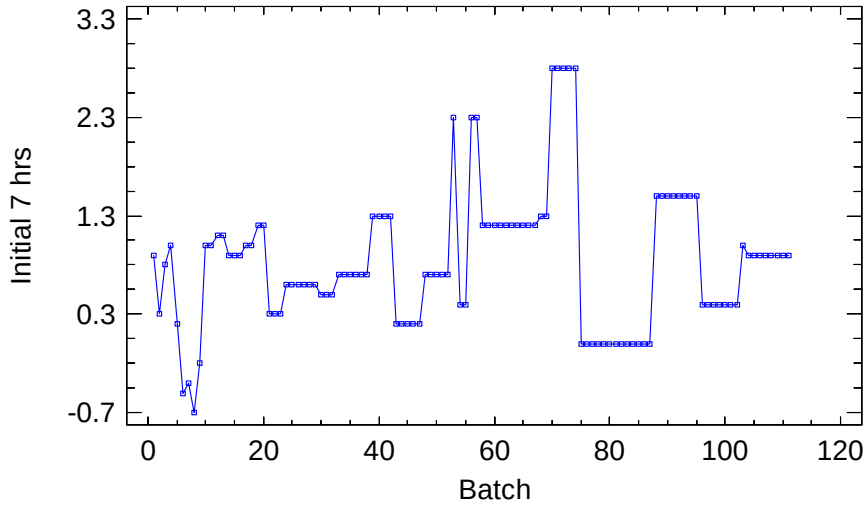

Figure 1. Initial 7 hour extraction for EP 75B (mean value = 0.86 mg/sq.in)

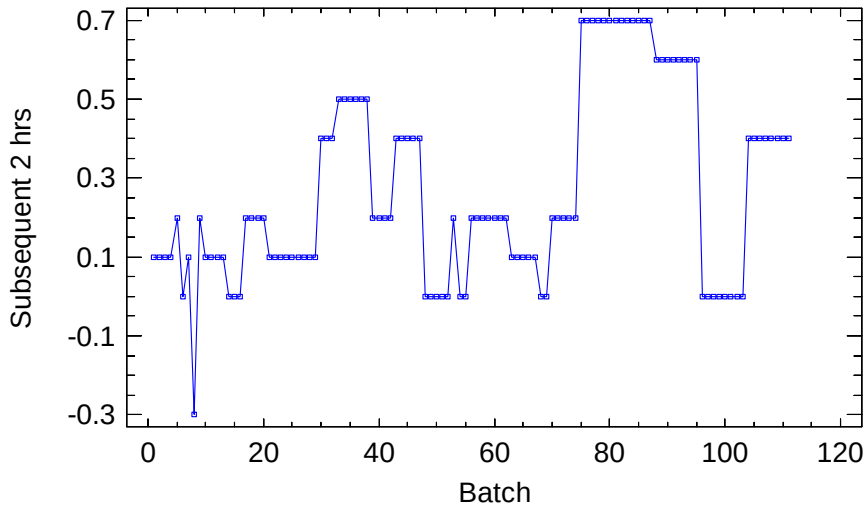

Figure 2. Secondary 2 hour extraction for EP 75B (mean = 0.27 mg/sq.in)

Elast-O-Pure EP 75B easily satisfies the criteria of this specification and work is underway to further tighten the limits for internal uses only. FDA CFR 177.2600 was chosen as it is internationally recognised, and crucially, it is a simple and easily implemented in routine test procedures.

Additional extraction tests have also been carried out to USP <381> and to customer specific requests, often in solvents other than water. This is returned to later in the paper.

Additional, more complex extraction testing, the author feels, must lie with the end user as only they know the precise chemistry of their process. This is particularly true for leaching studies, where each unique chemistry may result in a different set of leachable products. Additionally, the end user is better equipped to identify the leachables that are likely to be problematic, and at what levels, for their process.

Subject to the material meeting the criteria identified in JW 200 192, the material is then released to production for seal manufacture.

CLEAN ROOM MANUFACTURE

Cleanrooms are classified by the cleanliness of the air, as determined by the number of particles >0.5 microns in a cubic measurement of air. The original classification standard was Federal Standard 209 of the USA, this was later superseded by the international standard ISO 14644-1. Federal Standard 209 classifies a cleanroom as Class 10,000 i.e. less than 10,000 particles per cubic foot of air. ISO 14644-1 classifies a similar cleanroom as Class 7.

Currently James Walker & Co. Ltd. operate two cleanrooms, both validated to ISO Class 7 class 10,000), with particle count requirements of <352,000 per cubic metre, or <10,000 per cubic foot. Last validation report recorded an average particle count of 17,700 per cubic metre.

Once released from quarantine, having met all the criteria of JW 200 192, the material is released for production. Still sealed, the material is transferred to a Class 7 clean manufacturing, area before opening. Here it is slit or extruded, as required, depending on subsequent processing methods (injection or compression moulding).

Mould tooling has been specifically designed not only to mould the parts economically, but also for ease of cleaning, thereby reducing any possibility of contamination. Additionally, no mould release agents are employed in the manufacturing process, as these will undoubtedly increase extractables and leachables, and in many cases are known to be cytotoxic.

Once moulded the seals are finished, inspected, bagged, sealed and labelled before leaving the clean manufacturing area.

RESULTS

Having taken so much care to minimise any source of potential E & L, the question must be “Has it made a difference ?”

Extraction testing was carried out on seals that have gone through this manufacturing route, with samples taken at random from production runs, to determine the level of extractables.

The current test requirements for rubber articles for use in BioPharm processes are detailed in FDA 21 CFR 177.2600 and USP <381>.

<u>FDA 21 CFR 177.2600 Testing.</u>

The results of testing to this standard are shown in Table 1 below;

Sample	Weight loss after 7 hrs (mg/sq.in)	Weight loss after 7+2 hrs (mg/sq.in)
EP 75B	1.42	0.27
Competitor #1	1.77	N/A
Competitor #2	1.50	0.33
Competitor #3	2.02	2.16

Table 1.

These results for the JW product lie within the range determined on the base compound before going through the manufacturing process, and supports the use of these techniques in minimising extractable materials. Comparison with competitor products show the JW offering to be the cleanest material under this test.

USP <381> Testing.

The results of testing to this standard are shown in Table 2 below;

Sample	TOC (ppm)
EP 75B	61.2
Competitor #1	119
Competitor #2	138
Competitor #3	139

Table 2. Total Organic Carbon (TOC) as determined by USP <381>; 2 hrs, 121^{o}C, water.

Again the results are quite clear, that with proper care and attention to detail, the extractables in this test give approximately a 50% reduction in extractable material. Again this supports that the procedures adopted in manufacture result in a cleaner product.

Additional Testing.

In many instances, end users employ different solvents, particularly in pharmaceutical applications and extraction testing in the appropriate solvent is required. Table 3 below shows the results for an acetone extraction (1 hour reflux) and again shows the James Walker & Co. Ltd. product to be the cleaner product when compared to the competitor seals.

Sample	Acetone Extraction (wt %)
EP 75B	- 0.2
Competitor #1	- 1.2
Competitor #2	- 1.1
Competitor #3	- 3.2

Table 3.

Again, as this test was carried out on manufactured products, it strongly suggests that the care taken in manufacturing operations results in a cleaner product, with the nearest competitor still a factor of six higher than EP 75B.

REFLUX OR SOXHLET ?

There have been numerous debates as to how to perform any extraction test, and generally centre around solvent type, and the extraction method. In particular, the question of reflux or soxhlet extraction is often raised. Figure 3 shows a comparison between these two methods for EP75B in water.

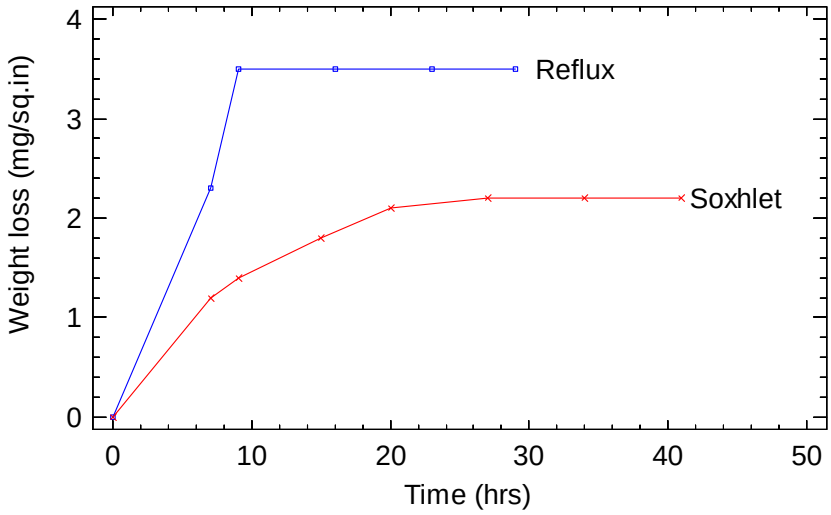

Figure 3. Extraction of EP 75B seal in water.

From the figure, for this material, we note two important points. Firstly, a limiting value is reached for both methods of extraction, and secondly the reflux extraction is more searching, giving a higher extraction value, and reaching the plateau faster. From a manufacturing viewpoint, reflux extraction is favoured as this is a more severe test, and yields results in a shorter period.

OTHER PERFORMANCE CRITERIA

It must be remembered that the E&L performance of the seal is only one of the performance criteria that must be met, as well as being a USP Class VI material. The material first and foremost must function as a seal, and the ability to do so is dependant on the material properties, as well as the seal design. The basic mechanical properties are shown below in Table 4.

Property	Unit	Value
Hardness	IRHD	76
Tensile Strength	MPa	16.4
Elongation at break	%	130
Compression Set 168 hours at 100°C	%	6.0
Compression Set 168 hours at 125°C	%	11.4

Table 4.

Other performance criteria are documented in the ASME BPE 2009 Standard, and include resistance to water for injection (WFI), clean in place (CIP) and steam in place (SIP). Tables 5, 6 and 7 below summarise the resistance of Elast-O-Pure EP75B to CIP and WFI, and show the material to perform well in these media.

Property	Unit	4 weeks at 80°C
Volume Change	%	+ 3.2
Change in tensile strength	%	+26
Change in elongation at break	%	+ 31
Change in hardness	IRHD	- 3

Table 5. Results in WFI

Property	Unit	4 weeks at 60°C
Volume Change	%	+ 2.6
Change in tensile strength	%	- 9.7
Change in elongation at break	%	- 7
Change in hardness	IRHD	- 2

Table 6. Results in CIP 100

Property	Unit	4 weeks at 20°C
Volume Change	%	+ 0.1
Change in tensile strength	%	- 24
Change in elongation at break	%	- 16
Change in hardness	IRHD	0

Table 7. Results in CIP 200

INTRUSION TESTING

One of the key seal performance criteria is that of intrusion, as defined by ASME BPE 2009 SG 2.4.1. The mechanism of intrusion is complex and depends on numerous factors including; seal design, material properties, applied load, and surface contact. However, its importance in Biopharmaceutical processing must not be underestimated, as poor intrusion performance can result in contamination and ineffective cleaning regimes.

Intrusion is a key parameter in the performance of a hygienic clamp seal, and will have a bearing on leachables determined, simply by exposing more of the seal to the process fluid. Intrusion can be defined as by how much the seal under load projects into the process flow relative to the pipe bore (see Figure 4).

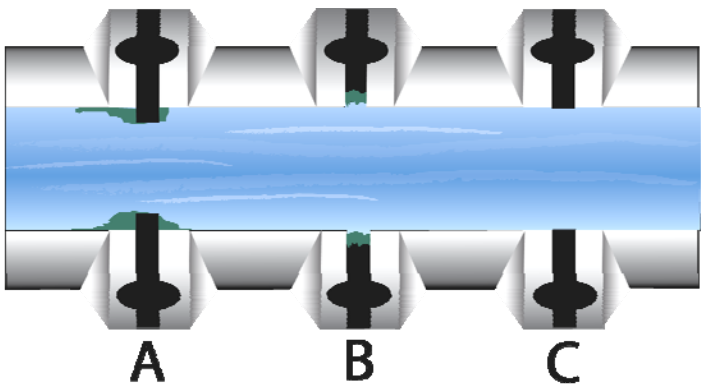

Figure 4. Schematic of intrusion.

In Figure 4, position A represents positive intrusion, where the seal is projected, under load, into the product flow path. This results in “dead spots” in the flow path where material from the process can build

up and lead to possible future contamination and difficulties in cleaning. Furthermore, by the mere fact that the rubber is protruding into the flow, it raises the possibility of rubber from the seal breaking away and contaminating the product. Position B, also referred to as negative intrusion, but more correctly recession, again leads to possible build up of material and subsequent potential cleaning and contamination problems. Position C represents the ideal, with zero intrusion, where no material build up is experienced.

In recognition of how important intrusion is to a Biopharmaceutical processor, the ASME BPE 2009 standard categorises intrusion (recession is assigned a negative value) into two categories; Category I defined as +/- 0.60 mm, and the more demanding Category II defined as +/- 0.20 mm.
Future editions of this standard aim to categorise intrusion further by including intrusion performance after numerous steam in place (SIP) cycles.

A non-mandatory section of this standard details the steam testing of gaskets up to 500 one hour long cycles, and measuring the resultant intrusion. The results are given in Table 8 below.

Seal	**No Cycles**		**100 Cycles**		**500 Cycles**	
	Category I	Category II	Category I	Category II	Category I	Category II
0.5”	0.11 mm 100%	0.11 mm 100%	0.29 mm 100%	0.29 mm 35%		
0.75”	0.14 mm 100%	0.14 mm 100%	0.45 mm 100%	0.45 mm 0%		
1.0”	-0.17 100%	-0.17 73%	0.49 mm 75%	0.49 mm 0%	0.60 mm 65%	0.60 mm 0%
1.5”	-0.36 mm 100%	-0.36 mm 0%	-0.57 mm 85%	-0.57 mm 0%		
2”	-0.54 mm 100%	-0.54 mm 0%	-0.67 mm 30%	-0.67 mm 0%		

Table 8. Intrusion per ASME-BPE 2009 SG-2.4.1

This is a very good result, which shows that even after 500 steam cycles, the gasket still meets Category I 65% of the time, and also demonstrates the long term stability of EP 75B. Additionally, this minimal intrusion minimises the surface area exposed to the process fluid, and consequently minimises the leachables determined.

Although, not part of the standard requirements, it was decided to investigate any weight changes throughout this test regime (Table 9).

	No Cycles	**100 Cycles**	**500 Cycles**
% Weight Change	N/A	-0.10%	-0.17%

Table 9. Weight loss on steam cycling.

This shows again the effect of extractables, this time in steam, and is still a very low figure. As to what these extractables are chemically, and whether these interfere with the process, or are indeed leachable in process fluids, still remains to be seen, and may form the basis for future studies.

CONCLUSION

Control of extractables and leachables is dependant upon a number of factors, starting with consideration of the purity of the ingredients, the reactive compounds and their solubility in contact media. Risks of contamination from other materials can be minimised by a process of risk assessment, ideally arising from a detailed FMEA. The resulting procedures should result in effective control of the process. The use of cleanrooms will avoid particulate contamination of the parts. Finally test procedures must be developed to reflect the quality characteristics important to the customer.

During product design, due consideration must also be given to the ability to operate in application, achieving a balance of physical as well as “clean” system operation.

James Walker

James Walker worldwide sales and customer support

James Walker Asia Pacific
Tel: +65 6777 9896
Fax: +65 6777 6102
Email: sales.sg@jameswalker.biz

James Walker Australia
Tel: +61 (0)2 9721 9500
Fax: +61 (0)2 9721 9580
Email: sales.au@jameswalker.biz

James Walker Benelux
(Belgium)
Tel: +32 3 820 7900
Fax: +32 3 828 5484
Email: sales.be@jameswalker.biz
(Netherlands)
Tel: +31 (0)186 633111
Fax: +31 (0)186 633110
Email: sales.nl@jameswalker.biz

James Walker Brasil
Tel: +55 11 4392 7360
Fax: +55 11 4392 5976
Email: sales.br@jameswalker.biz

James Walker China
Tel: +86 21 6876 9351
Fax: +86 21 6876 9352
Email: sales.cn@jameswalker.biz

James Walker Deutschland
Tel: +49 (0)40 386 0810
Fax: +49 (0)40 389 3230
Email: sales.de@jameswalker.biz

James Walker France
Tel: +33 (0)437 497 480
Fax: +33 (0)437 497 483
Email: sales.fr@jameswalker.biz

James Walker Iberica
Tel: +34 94 447 0099
Fax: +34 94 447 1077
Email: sales.es@jameswalker.biz

James Walker Inmarco (India)
Tel: +91 (0)22 4080 8080
Fax: +91 (0)22 2859 6220
Email: info@jwinmarco.com

James Walker Ireland
Tel: +353 (0)21 432 3626
Fax: +353 (0)21 432 3623
Email: sales.ie@jameswalker.biz

James Walker Italiana
Tel: +39 02 257 8308
Fax: +39 02 263 00487
Email: sales.it@jameswalker.biz

James Walker Mfg (USA)
Tel: +1 708 754 4020
Fax: +1 708 754 4058
Email: sales.jwmfg.us@jameswalker.biz

James Walker New Zealand
Tel: +64 (0)9 272 1599
Fax: +64 (0)9 272 3061
Email: sales.nz@jameswalker.biz

James Walker Norge
Tel: +47 22 706800
Fax: +47 22 706801
Email: sales.no@jameswalker.biz

James Walker Oil & Gas (USA)
Tel: +1 281 875 0002
Fax: +1 281 875 0188
Email: oilandgas@jameswalker.biz

James Walker South Africa
Tel: +27 (0)31 304 0770
Fax: +27 (0)31 304 0791
Email: sales.za@jameswalker.biz

James Walker UK
Tel: +44 (0)1270 536000
Fax: +44 (0)1270 536100
Email: sales.uk@jameswalker.biz

JW4473 0910/pdf

www.jameswalker.biz

Registered Office: James Walker Sealing Products and Services Ltd, Lion House, Oriental Road, Woking, Surrey GU22 8AP, United Kingdom. Reg No. 00264191 England