WHITE PAPER

Why talc pleurodesis with STERITALC® remains the method of choice.

The importance of particle size in talc.

Boston Medical Products
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Talc – why size matters

As the world's most commonly used pleurodesis agent today, talc boasts the largest body of evidence on efficacy and the most comprehensively evaluated and evidenced adverse events profile. While talc remains the pleurodesis agent of choice in patients with malignant pleural effusions, (1-4) its use remains controversial – largely due to unfounded concerns regarding cases of acute respiratory distress syndrome (ARDS) reported in the literature. Most reports of ARDS have emanated from studies conducted in North America and the UK, which primarily use small-particle, non-calibrated talc and/or doses up to and exceeding 10 g per hemithorax.[1–4] Large studies from Europe and Israel showed no links with ARDS.[5–7]

A clear dose effect on extrapleural talc dissemination and, hence, inflammation and ARDS in the contralateral lung has since been demonstrated in animal studies in rodents.[8] Similarly, clinical trial data not only support the hypothesis that hypoxemia and ARDS following talc pleurodesis are linked to lung and systemic inflammation, but also suggest that intercountry differences in the incidence of ARDS may be linked to talc particle size.[9] Similar results have been reported elsewhere.[10]

Talc composition

Motivated by the desire to investigate the reasons underlying marked geographical differences in ARDS prevalence following intrapleural talc administration, Ferrer et al. (2001)[11] conducted an analysis of eight talc preparations. Their aim was to establish whether intercountry differences might be due to one or more of the characteristics of the talc preparations used. Using a Laser Mastersizer/E particle size analyzer, the authors determined the chemical composition and particle size distributions for talc products from eight different suppliers: four from the United States, and one each from Spain, France, Taiwan and Brazil.

Talc products differ markedly across the globe

Table 1A (adapted from Ferrer et al. (2001)[11]

Talc source*	Mean diameter, µm	Median (Dv(50), µm	Dv(10), µm	Dv(90), µm
US talc A	10.8	7.8	2.4	22.7
US talc B	19.4	13.2	3.2	46.8
US talc C	20.1	13.5	3.1	49.5
Spain	20.1	14.8	3.7	45.7
US talc D	20.4	13.9	3.1	49.4
Brazil	25.4	21.5	6.4	50.5
Taiwan	32.3	28.7	7.2	64.4
France	33.6	31.3	10.5	60.6

* Talc A: Sigma Chemicals; Saint Louis, MO. Talc B: Malinckrodt; Chesterfield, MO. Talc C: J.T. Baker; Phillipsburg, PA. Talc D: Integra Chemical; Renton, WA. Spain: Luzenac talc; Ditalc; Barcelona, Spain. France: Luzenac Europe; Toulouse, France. Taiwan: Merck Taiwan LTD; Taipei, Taiwan. Brazil: Xilolite; Sao Paulo, Brazil)

Table 1B (adapted from: Navarro Jiménez et al. 2005, p. 200)[12]

Talc source	Mean particle size, µm	Particles < 5 µm	Particles < 10 µm
Brazil	7.2	54%	84%
USA	9.4	54%	81%
Spain	9.8	56%	81%
France	17.3	33%	60%
Brazil	18.4	32%	51%
France (STERITALC®)	26.2	4%	10%
Brazil	30.3	15%	31%

The researchers' data (Table 1A, page 3) showed marked differences in particle size distributions.* As suspected, based on the higher incidence of ARDS in the US, the average particle size of US-based products tended to be significantly smaller than non-US products. They also tended to include much finer particles than non-US talc products.

These findings were mirrored by Navarro Jiménez et al. (2005),[12] who tested 14 different talc products (9 from Brazil, 3 from France, 1 from Spain and 1 from the United States). (Table 1B)

Both sets of data demonstrate the inadequacy of 'mean particle size' as a single measure of particle size distribution. In Table 1A, for instance, the talc products with the largest means (Taiwan and France) differed considerably in terms of their overall particle size distributions, as expressed by the 10th and 90th percentile values (or Dv(10) and Dv(90)†). While 10% of the French product contains particles of size 10.5% or smaller, the smallest 10% of the Taiwanese product contains particles of size 7.2 µm or smaller. Given that small particle size talc (< 10 µm) has been repeatedly implicated in serious and severe post-pleurodesis complications,[13–16] this difference in the proportions of very small, 'high-risk' particles may be an important indicator of the true risk level associated with a particular talc product.

Let's talk talc

"Talc is a naturally occurring mineral, mined from the earth, composed of magnesium, silicon, oxygen, and hydrogen. Chemically, talc is a hydrous

* The products also showed marked differences in terms of impurities present. The hypothesis that acute lung injury might be due to these impurities rather than the talc itself appeared plausible at the time. However, this hypothesis was subsequently laid to rest by Maskell et al. (2004), whose RCT comparing the effects of mixed and graded talc involved the use of physically different but chemically identical talc products from the same manufacturer (Maskell et al. 2004).

† The Dv(50) – also known as the median – indicates the size point below which 50% of the material is contained. Similarly, the Dv(10) indicates the size point below which 10% of the material is contained. Consequently, if the Dv(10) is 10.7, this means that 10% of the sample has a size of 10.7µm or smaller. The Dv(90) is the size point below which 90% of the material is contained (and provides some information on the size and proportion of the largest particles contained in the sample).

magnesium silicate with a chemical formula of $Mg_3Si_4O_{10}(OH)_2$."‡ Given the vast differences in physical and chemical composition of talc products around the world,[11,12] in addition to the wide range of applications (medical, cosmetic, industrial), the absence of a standardized definition of 'talc' may not come as a surprise. What does come as a surprise, however, is the following:

There is no standardized definition of the type of talc product suitable for use in pleurodesis.

In the United States, for instance, the FDA has so far only issued draft guidance on talc, providing nonbinding recommendations regarding testing to determine particle size distribution.§ In other areas of the world (where medical grade may

be inaccessible or too expensive), no distinction is made between medical-grade talc and talc for cosmetic use. Agarwal et al. (2011)[17] conducted a randomized controlled trial comparing cosmetic talc with iodopovidone in patients with recurrent pleural effusions and/or spontaneous pneumothorax. Only minor side effects were observed in both groups, and none of the patients experienced hypotension or ARDS. In contrast to many cosmetic talc products, the product used by Agarwal et al. was reported to have been akin to a large-particle talc, its size given as "20-60µm". However, the authors later specified the use of scanning electron microscopy (SEM) to ascertain "average particle size", suggesting that the value range is more likely to be referring to the interquartile range, i.e. the 'middle fifty percent' of the distribution. This would mean that 25% of the product by volume contains particles < 20 µm. None of this provides any information on the actual range of dimensions (largest and smallest particles) or their relative proportions (including of particles < 20 µm).

High-risk vs low-risk talc?

Most early reports of ARDS originated in countries where preparations including small particle sizes are prevalent.[1,18,19] In contrast, large observational studies from countries that routinely use large-particle talc products reported only few serious adverse events.[5,20] While it has long been hypothesized that reports of observed toxicity may relate to the use of talc preparations that include small particles (<15 µm), the link remains difficult to corroborate, given that most talc-related research in humans does not provide details of either the talc product used or meaningful information pertaining to particle size distribution (Table 2, page 6). Some researchers (e.g., Gonzales et al. 2010[14]) mention the product used (in their case Sclerosol) but provide no mean or median particle size nor information on particle size distribution. As a result, adverse events directly linked to particle size and/or talc dose are impossible to disentangle and continue to be ascribed to talc per se, despite the well-known and marked variations in the substance's chemical and physical characteristics.

‡ U.S. Food & Drug Administration (FDA) website. "Talc" (last updated 12/07/2022). https://www.fda.gov/cosmetics/cosmetic-ingredients/talc [last accessed 12 March 2023]

§ U.S. Food & Drug Administration (FDA) website. "Draft Guidance on Talc" (version date August 2020). https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_205555.pdf [last accessed 13 March 2023]

Table 2: Lack of consistency in size-based categorization of talc products used in research studies

Article	Talc used	Size category	Particle size information	Comments
Arellano-Orden et al. 2013[24]	Instituto EspañolTM (Seville, Spain)	'Small particle talc', approximately 50% of particles < 10	mean ± SD median [10-90%] 15.9 ± 13.9 11.5 [2.7 – 35.9]	103 patients **1 case of ARDS**
	STERITALC®(Novatech, La Ciotat, France	'Large-particle talc', approximately 20% of particles < 10 µm	25.3 ± 16.5 22.8 [5.6 – 48.1]	124 patients **No ARDS**
Maskell et al. 2004[9]	Thornton and Ross, Huddersfield, UK	'Mixed talc', typical of that used in the US&UK	including 50% of particles < 15 µm	more lung and systemic inflammation & hypoxemia than with graded talc
	Novatech, Grasse, France	'Graded talc', typical of that used in continental Europe	including 50% of particles > 25 µm, most particles < 10 µm have been removed	
Janssen et al. 2007[22]	STERITALC®, Novatech	'calibrated French large-particle talc' (4 g)	"mean particle size of this talc preparation is 24·5 µm. The concentration of small particles (<5 µm) in STERITALC® is 11% by volume"	558 patients **No ARDS**
Barbetakis et al. 2010[25]	--	Sterile asbestos-free talc powder (6 g)	--	400 patients **7 cases of ARDS**
Bridevaux et al. 2011[26]	STERITALC®	'graded talc (…) "> 10 mm and should contain only a small percentage of smaller particles. Thus, particles with a diameter of 6 µm have little or no ability to cross pleural stomata."		418 patients **No ARDS**
Agarwal et al. 2011[17]	'cosmetic talc'	--	(interquartile?) range 20 – 60 µm	34 patients **No ARDS**
Viallat et al. 1996[7]	Asbestos-free talc from Luzenac (France)	--	--	327 patients **No ARDS**
Shinno et al. 2017[21]	--	'large particle size talc (4 g or less)	--	27 patients **4 cases of ARDS**
de Campos et al. 2001[23]	Asbestos-free talc Sterifarma Lab, Sao Paulo,Brazil		"particle size of 5 to 70 µm". No information on particle size distribution or proportion of particles < 10 µm	614 patients **7 cases of ARDS**

Table 3: Talc products with a mean particle size of > 25 µm

Source	Talc/Provenance	Mean diameter, µm	Median, µm	Dv(10), µm	Particles <10 µm
Ferrer et al. 2001[11]	Brazil	25.4	21.5	6.4	
	Taiwan	32.3	28.7	7.2	
	France	33.6	31.3	10.5	
Navarro-Jiménez et al. 2005[12]	Brazil	30.3			31%
	France (STERITALC®)	26.2			10%
STERITALC® lab reports*	STERITALC®		28.64	10.72	
	Pharmaceutical talc product		25.75	6.51	

Other researchers have attempted to establish simple definitions in order to distinguish between small-particle and large-particle talcs. Maskell et al.,[9] for instance, described the two talc products used in their RCTs as 'mixed talc' (with a mean particle size of < 15 µm) and 'graded talc' (with a mean particle size of > 25 µm, most particles < 10 µm having been removed). Using the data by Ferrer et al.[11] in Table 1A, one can see clearly that only one of the products listed would have qualified as 'graded' talc using this definition. The same goes for the data by Navarro Jiménez et al.[12] in Table 1B.

Unfortunately, particle size-based categorization is not underpinned by any standardized rules or definitions. Maskell et al.'s 'graded talc'[9] differs dramatically from Arellano-Orden et al.'s 'large-particle talc',[10] the former containing less than 10% of particles smaller than 10µm, the latter containing "approximately 20 %" of particles smaller than 10 µm. Similarly, Shinno et al.[21] state that they used 'large-particle talc' in their small study with an unusually high incidence of ARDS. However, they fail to specify both the product's name and all crucial details such as the product's mean and/or median particle size and the proportion of particles under 10 µm. This omission appears to be the rule rather than the exception: a realization that led Janssen et al.[22] to comment that "of the publications that described acute respiratory distress syndrome after talc pleurodesis, details of the particle size of the talc were given only in one" (Janssen et al. 2007,[22] p. 1538).

* See Appendix I at the end of this document.

In the USA, STERITALC® is approved as a pharmaceutical product.

The research referred to by Janssen et al. was a 2001 study by de Campos et al.[23] who reported seven cases of ARDS in their large series of patients treated with "2 g of asbestos-free talc or hydrated magnesium silicate ($Mg_3Si_4O_{10}[OH]_2$ with a particle size of 5 to 70 µm (Sterifarma Lab; Sao Paulo, Brazil)" (de Campos et al. 2001,[23] p. 802). Unfortunately, the authors did not provide details of the talc product's particle size distribution or the proportion of very small particles present. Given previously published data on talc products from Brazil (Tables 1A and 1B),[11,12] it is highly unlikely that the product used would have qualified as either a graded talc or a large-particle talc. Table 2 provides a useful overview of the confusion caused by this complete lack of standardization, consensus and convention.

In contrast to the lack of essential detail in the research reporting ARDS following talc pleurodesis, there is a remarkable evidence base discounting a link between STERITALC® and ARDS. A large clinical trial evaluating 558 patients treated with STERITALC® 4 g by poudrage for MPE reported no cases of ARDS or talc-related injury.[22] Nor did a large prospective study involving 418 patients with recurrent primary spontaneous pneumothorax treated with STERITALC® 2 g by poudrage.[26]

Numerous studies evaluating the efficacy and/or safety of STERITALC® have been published over the years. None has reported cases of ARDS.[7,9,22,26–39]

Graded/calibrated talc

By demonstrating that talc pleurodesis using talc with a mean particle size of less than 15 µm ("mixed" talc) produces more lung and systemic inflammation than tetracycline or "graded" talc – which not only has a median particle size of > 25 µm but has also had the majority of small particles under 10 µm removed – Maskell et al.[9] appear to have set a benchmark for large-particle, graded (or calibrated) talc. In the literature,

this is often understood to mean a mean particle size of > 25 µm, and tends to be referred to as 'large-particle', 'graded' or 'calibrated' talc. While these terms are often used interchangeably, they can refer to products with very different characteristics (Table 3, page 7).

In addition to showing that means and medians can differ markedly, Table 3 also demonstrates that

only STERITALC® can currently claim to meet the graded talc/calibrated talc benchmark established by Maskell et al. (2004):[9] the product includes "50% of particles > 25 µm", and "most particles < 10 µm have been removed".

Notably, STERITALC® laboratory reports confirm that STERITALC® has a controlled particle size to minimize the risk of acute pneumonitis and ARDS. Active control of small particles results in a median particle size of > 28 µm and a Dv(10) of 10.72 µm. Comparisons were made with a competitor product that describes itself as conforming "with the monograph 0438 of the current European Pharmacopoeia", with a "controlled particle size" and an "average particle size" of "26 µm". When subjected to the same particle size testing as STERITALC®, the product failed on a number of parameters, including Dv(10) (Table 3; also Table 4, Appendix I), meaning it has not had "most particles < 10 µm" removed. Consequently, it does not meet the requirements of a size-controlled talc product.

Lack of consistency harms science – and may harm patients

Consistency in how terminology is used matters. Inconsistencies in the use of clearly defined entities such as 'mean' and 'median' create confusion for researchers and make the interpretation of available data difficult to impossible. The lack of any official definitions of terms such as "graded", "calibrated" and "large-particle" talc, and the tendency for researchers to use the terms interchangeably, creates a real problem. Vast numbers of (often retrospective) studies linking talc with complications including ARDS may be misinterpreted as extending to talc per se, regardless of its chemical or physical composition.

Similarly, the many studies confirming the safety of STERITALC® as a truly size-controlled talc product may be misinterpreted as extending to any talc product claiming to be a size-controlled/calibrated/graded product.

Test results for the 'pharmaceutical talc product' reported in Table 3 - alongside the particle size distribution graphs comparing STERITALC and the 'pharmaceutical talc product' in Appendix II - confirm that this is simply not the case. It is therefore perhaps time to use more meaningful particle size distribution data, which are capable of providing information not only on means and medians, but also on the proportion of 'high-risk' particles, expressed either as Dv(10) or the percentage of particles under 10 µm.

NOVATECH STERITALC® is a sterile talcum powder which is mined in FRANCE and specifically processed for medical use. The product undergoes additional, sophisticated production steps which actively eliminate small particles in order to minimize the risk of ARDS. This ensures the product maintains a mean particle size of > 28µm and contains less than 10% of particles < 10 µm.

A note on averages

What does 'mean' mean?

There is evidence to suggest that researchers may be using the terms 'mean' and 'median' interchangeably. As mentioned in the text, Maskell et al. defined the two talc products used as part of their 2004 RCTs as follows:

Mixed talc **"mean particle size of less than 15 µm"**

Graded talc **"mean particle size of > 25 µm" and "had the majority of particles less than 10 µm size removed".**

Unfortunately, the authors also use a second definition, namely:

Mixed talc **"including 50% of particles < 15 µm**

Graded talc **"including 50% of particles > 25 µm" and "most particles < 10 µm have been removed"**

Given that the median is the data point which separates the lower and higher 50% of the sample, the second definition indicates that their size requirement relates to the median rather than the mean. This would suggest that they are using the two terms interchangeably, which poses a real problem.

For instance, Ferrer et al. (2001) examined a range of talcum products from different countries (using a Mastersizer/E particle analyzer). They recorded both mean and median values as well as the 10th and 90th percentiles, to provide information on the particle distribution within the samples.

	Mean diameter	Median diameter	10th percentile	90th percentile
STERITALC®	33.6 µm	31.3 µm	10.5 µm	60.6 µm
Brazil	25.4 µm	21.5 µm	6.4 µm	50.5 µm

The measured means of both the talc products listed above (STERITALC® and a talc from Brazil) fulfill Maskell et al.'s primary requirement of a 'graded talc' product of a "mean particle size > 25 µm". However, only one of these products (STERITALC®) meets the second definition of "including 50% of particles > 25 µm" (i.e., a median of > 25 µm). Similarly, the 10th percentile data show that only STERITALC® fulfills the secondary requirement of having had "the majority of particles less than 10 µm" removed.

Navarro-Jiménez, who analyzed a total of 14 talc products (using computerized image analysis of photographs taken using optical microscopy under polarized light and electron microscopy), recorded (among other things) mean particle sizes and the percentage of particles smaller than 10 µm. A comparison of STERITALC® with a talc product from Brazil looked as follows:

	Mean diameter	Particles < 10 µm
STERITALC®	26.2 µm	10%
Brazil	30.3 µm	31%

At first glance (and if only using mean diameter), the Brazil talc meets the requirement of a 'graded talc' according to the means-based definition used by Maskell et al. 2004. In fact, its mean is larger than that of STERITALC® in this comparison. What the 'mean' as a statistical measure hides, however, is the particle distribution. For instance, if the Brazil talc has a larger proportion of large particles or a larger proportion of much larger particles than STERITALC®, this will increase its mean particle size. A larger proportion of large particles can thus mask a larger proportion of small particles. In this particular case, almost a third of particles in the Brazil talc are smaller than 10 µm, compared to just 10 % in STERITALC®. Adding the 10th and 90th percentile values provides information on the minimum and maximum particle sizes (range) and the relative proportions of smaller and larger particles within the sample.

	Mean diameter	Particles < 10 µm	10th percentile	90th percentile
STERITALC®	26.2 µm	10%	7.13	52.93
Brazil	30.3 µm	31%	6.55	61.12

In addition to demonstrating that values obtained (including the mean and median) will vary depending on the method of particle size analysis used, these data also demonstrate why 'average particle size' should always be expressed using both mean and median values: either value alone does not provide sufficient information on the shape of the particle size distribution. Ideally, the mean and median values should be accompanied by the 10th and 90th percentiles (aka Dv(10) and Dv(90)) as these add meaningful information on the shape of the particle size distribution and, hence, the proportion of larger/smaller particles contained within the sample.

References

1. Rehse DH, Aye RW, Florence MG. Respiratory failure following talc pleurodesis. Am J Surg. 1999;177(5):437-440. doi:10.1016/s0002-9610(99)00075-6
2. Rinaldo JE, Owens GR, Rogers RM. Adult respiratory distress syndrome following intrapleural instillation of talc. J Thorac Cardiovasc Surg. 1983;85(4):523-526.
3. Colt HG, Davoudi M. The ideal pleurodesis agent: still searching after all these years. Lancet Oncol. 2008;9(10):912-913. doi:10.1016/S1470-2045(08)70239-0
4. Lee YCG, Baumann MH, Maskell NA, et al. Pleurodesis practice for malignant pleural effusions in five English-speaking countries: survey of pulmonologists. Chest. 2003;124(6):2229-2238. doi:10.1378/chest.124.6.2229
5. Weissberg D, Ben-Zeev I. Talc pleurodesis. Experience with 360 patients. J Thorac Cardiovasc Surg. 1993;106(4):689-695.
6. Cardillo G, Facciolo F, Carbone L, et al. Long-term follow-up of video-assisted talc pleurodesis in malignant recurrent pleural effusions. Eur J Cardiothorac Surg. 2002;21(2):302-305; discussion 305-306. doi:10.1016/s1010-7940(01)01130-7
7. Viallat JR, Rey F, Astoul P, Boutin C. Thoracoscopic talc poudrage pleurodesis for malignant effusions. A review of 360 cases. Chest. 1996;110(6):1387-1393. doi:10.1378/chest.110.6.1387
8. Montes JF, Ferrer J, Villarino MA, Baeza B, Crespo M, Garcia-Valero J. Influence of talc dose on extrapleural talc dissemination after talc pleurodesis. Am J Respir Crit Care Med. 2003;168(3):348-355. doi:10.1164/rccm.200207-767OC
9. Maskell NA, Lee YCG, Gleeson FV, Hedley EL, Pengelly G, Davies RJO. Randomized trials describing lung inflammation after pleurodesis with talc of varying particle size. Am J Respir Crit Care Med. 2004;170(4):377-382. doi:10.1164/rccm.200311-1579OC
10. Arellano-Orden E, Romero-Falcon A, Juan JM, Ocaña Jurado M, Rodriguez-Panadero F, Montes-Worboys A. Small particle-size talc is associated with poor outcome and increased inflammation in thoracoscopic pleurodesis. Respiration. 2013;86(3):201-209. doi:10.1159/000342042
11. Ferrer J, Villarino MA, Tura JM, Traveria A, Light RW. Talc preparations used for pleurodesis vary markedly from one preparation to another. Chest. 2001;119(6):1901-1905. doi:10.1378/chest.119.6.1901
12. Navarro Jiménez C, Gómez Izquierdo L, Sánchez Gutierrez C, et al. Análisis morfométrico y mineralógico de 14 muestras de talco usado para pleurodesis en distintos países de europayamérica* / Morphometric and mineralogical análisis of 14 samples of talc used for pleurodesis in several european and american countries. Neumosur. 2005;17:197-202.
13. Ferrer J, Montes JF, Villarino MA, Light RW, García-Valero J. Influence of particle size on extrapleural talc dissemination after talc slurry pleurodesis. Chest. 2002;122(3):1018-1027. doi:10.1378/chest.122.3.1018
14. Gonzalez AV, Bezwada V, Beamis JF, Villanueva AG. Lung injury following thoracoscopic talc insufflation: experience of a single North American center. Chest. 2010;137(6):1375-1381. doi:10.1378/chest.09-2020
15. Genofre EH, Vargas FS, Acencio MMP, Antonangelo L, Teixeira LR, Marchi E. Talc pleurodesis: evidence of systemic inflammatory response to small size talc particles. Respir Med. 2009;103(1):91-97. doi:10.1016/j.rmed.2008.07.021
16. Dresler CM, Olak J, Herndon JE, et al. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. Chest. 2005;127(3):909-915. doi:10.1378/chest.127.3.909
17. Agarwal R, Paul AS, Aggarwal AN, Gupta D, Jindal SK. A randomized controlled trial of the efficacy of cosmetic talc compared with iodopovidone for chemical pleurodesis. Respirology. 2011;16(7):1064-1069. doi:10.1111/j.1440-1843.2011.01999.x
18. Kennedy L, Rusch VW, Strange C, Ginsberg RJ, Sahn SA. Pleurodesis using talc slurry. Chest. 1994;106(2):342-346. doi:10.1378/chest.106.2.342
19. Campos JR, Werebe EC, Vargas FS, Jatene FB, Light RW. Respiratory failure due to insufflated talc. Lancet. 1997;349(9047):251-252. doi:10.1016/S0140-6736(05)64860-X
20. Rodriguez-Panadero F, Antony VB. Pleurodesis: state of the art. Eur Respir J. 1997;10(7):1648-1654. doi:10.1183/09031936.97.10071648
21. Shinno Y, Kage H, Chino H, et al. Old age and underlying interstitial abnormalities are risk factors for development of ARDS after pleurodesis using limited amount of large particle size talc. Respirology. 2017;23(1):55-59. doi:10.1111/resp.13192
22. Janssen JP, Collier G, Astoul P, et al. Safety of pleurodesis

with talc poudrage in malignant pleural effusion: a prospective cohort study. Lancet. 2007;369(9572):1535-1539. doi:10.1016/S0140-6736(07)60708-9

23. de Campos JR, Vargas FS, de Campos Werebe E, et al. Thoracoscopy talc poudrage : a 15-year experience. Chest. 2001;119(3):801-806. doi:10.1378/chest.119.3.801
24. Arellano-Orden E, Romero-Falcon A, Juan JM, Ocaña Jurado M, Rodriguez-Panadero F, Montes-Worboys A. Small particle-size talc is associated with poor outcome and increased inflammation in thoracoscopic pleurodesis. Respiration. 2013;86(3):201-209. doi:10.1159/000342042
25. Barbetakis N, Asteriou C, Papadopoulou F, et al. Early and late morbidity and mortality and life expectancy following thoracoscopic talc insufflation for control of malignant pleural effusions: a review of 400 cases. J Cardiothorac Surg. 2010;5:27. doi:10.1186/1749-8090-5-27
26. Bridevaux PO, Tschopp JM, Cardillo G, et al. Short-term safety of thoracoscopic talc pleurodesis for recurrent primary spontaneous pneumothorax: a prospective European multicentre study. Eur Respir J. 2011;38(4):770-773. doi:10.1183/09031936.00189710
27. Diacon AH, Wyser C, Bolliger CT, et al. Prospective randomized comparison of thoracoscopic talc poudrage under local anesthesia versus bleomycin instillation for pleurodesis in malignant pleural effusions. Am J Respir Crit Care Med. 2000;162(4 Pt 1):1445-1449. doi:10.1164/ajrccm.162.4.2002030
28. Kolschmann S, Ballin A, Gillissen A. Clinical efficacy and safety of thoracoscopic talc pleurodesis in malignant pleural effusions. Chest. 2005;128(3):1431-1435. doi:10.1378/chest.128.3.1431
29. Pletinckx P, Muysoms F, De Decker C, Daeter E, Claeys D. Thoracoscopic talc pleurodesis for the treatment of spontaneous pneumothorax. Acta Chir Belg. 2005;105(5):504-507. doi:10.1080/00015458.2005.11679768
30. Debeljak A, Kecelj P, Triller N, et al. Talc pleurodesis: Comparison of talc slurry instillation with thoracoscopic talc insufflation for malignant pleural effusions. Published online 2006:5.
31. Froudarakis ME, Klimathianaki M, Pougounias M. Systemic inflammatory reaction after thoracoscopic talc poudrage. Chest. 2006;129(2):356-361. doi:10.1378/chest.129.2.356
32. Ishida A, Nakamura M, Miyazawa T, Astoul P. Novel approach for talc pleurodesis by dedicated catheter through flexi-rigid thoracoscope under local anesthesia. Interact Cardiovasc Thorac Surg. 2011;12(5):667-670. doi:10.1510/icvts.2010.263137
33. Mármol Cazas EE, Martínez Somolinos S, Baldó Padró X, Rubio Garay MM, Penagos Tafurt JC, Sebastián Quetglás F. Efficacy, Mortality and Morbidity of Surgical Treatment of a Primary Spontaneous Pneumothorax by Videothorascopic Talc Pleurodesis. Cir Esp. 2011;89(7):463-467. doi:10.1016/j.cireng.2011.02.001
34. Mohsen TA, Zeid AAA, Meshref M, et al. Local iodine pleurodesis versus thoracoscopic talc insufflation in recurrent malignant pleural effusion: a prospective randomized control trial. Eur J Cardiothorac Surg. 2011;40(2):282-286. doi:10.1016/j.ejcts.2010.09.005
35. Basso SMM, Mazza F, Marzano B, Santeufemia DA, Chiara GB, Lumachi F. Improved quality of life in patients with malignant pleural effusion following videoassisted thoracoscopic talc pleurodesis. Preliminary results. Anticancer Res. 2012;32(11):5131-5134.
36. Keeratichananont W, Kaewdech A, Keeratichananont S. Efficacy and safety profile of autologous blood versus talc pleurodesis for malignant pleural effusion: a randomized controlled trial. Ther Adv Respir Dis. 2018;12:1753466618816625. doi:10.1177/1753466618816625
37. Kleontas A, Sioga A, Pandria N, et al. Clinical factors affecting the survival of patients diagnosed with non-small cell lung cancer and metastatic malignant pleural effusion, treated with hyperthermic intrathoracic chemotherapy or chemical talc pleurodesis: a monocentric, prospective, randomized trial. J Thorac Dis. 2019;11(5):1788-1798. doi:10.21037/jtd.2019.05.25
38. Chang Y, Cho D, Cho K, Cho M. Viscum pleurodesis is as effective as talc pleurodesis and tends to have less adverse effect. Support Care Cancer. 2020;28(11):5463-5467. doi:10.1007/s00520-020-05405-0
39. Foo CT, Pulimood T, Knolle M, Marciniak SJ, Herre J. Ambulatory Thoracoscopic Pleurodesis Combined With Indwelling Pleural Catheter in Malignant Pleural Effusion. Front Surg. 2021;8:738719. doi:10.3389/fsurg.2021.738719

Appendix I

STERITALC® volume-based particle size distribution is determined by laser scattering and wet dispersion according to USP <429>. The instrument used for this analysis is the Malvern Mastersizer 300.

Table 4A: STERITALC® particle size distribution data (STERITALC®'s own benchmark data are indicated by "required"; values which pass the benchmark test are shown in green)

		DV(10)*	Dv(25)*	Dv(50)*	Dv(75)*	Dv(95)*
Abbreviated Test ID	Required (µm) / Measured (µm)	9.3 – 13.42	15 – 19.82	24.2 – 31	36.5 – 46.2	61.1 – 76.24
#04_31401_2	M†	**10.6**	18.5	**28.9**	43.2	74.0
#03_31402_2	M†	**10.4**	18.3	**28.4**	41.8	66.7
#02_31327_2	M†	**10.7**	18.6	**28.7**	42.1	67.0
#04_30979_3	M†	**10.9**	18.7	**28.8**	42.1	67.1
#03_30757_1	M†	**10.4**	18.3	**28.3**	41.2	64.5
#04_30756 _1	M†	**10.7**	18.6	**28.7**	42.1	67.1
#02_30150_2	M†	**11.1**	18.9	**29.1**	42.4	66.8
#03_30148_2	M†	**10.6**	18.4	**28.4**	41.5	65.2
#04_30146_2	M†	**10.9**	18.7	**28.8**	42.2	67.1
#02 30150_1	M†	**10.9**	18.8	**28.8**	42.0	65.6
#-03 30148_1	M†	**10.7**	18.5	**28.4**	41.5	64.9
#04_30146_1	M†	**10.7**	18.5	**28.4**	41.6	65.9
	Average	**10.72**	18.57	**28.64**	42.05	66.83

* Dv(x) - the point in the size distribution, up to and including which, x% of the total volume of material in the sample is 'contained'.

† Measured (µm)

Table 4B: A pharmaceutical-grade talcum product with a mean particle size of > 25 µm tested against the STERITALC® benchmark values (STERITALC®'s own benchmark data are indicated by "required"; values which pass the benchmark test are shown in green)

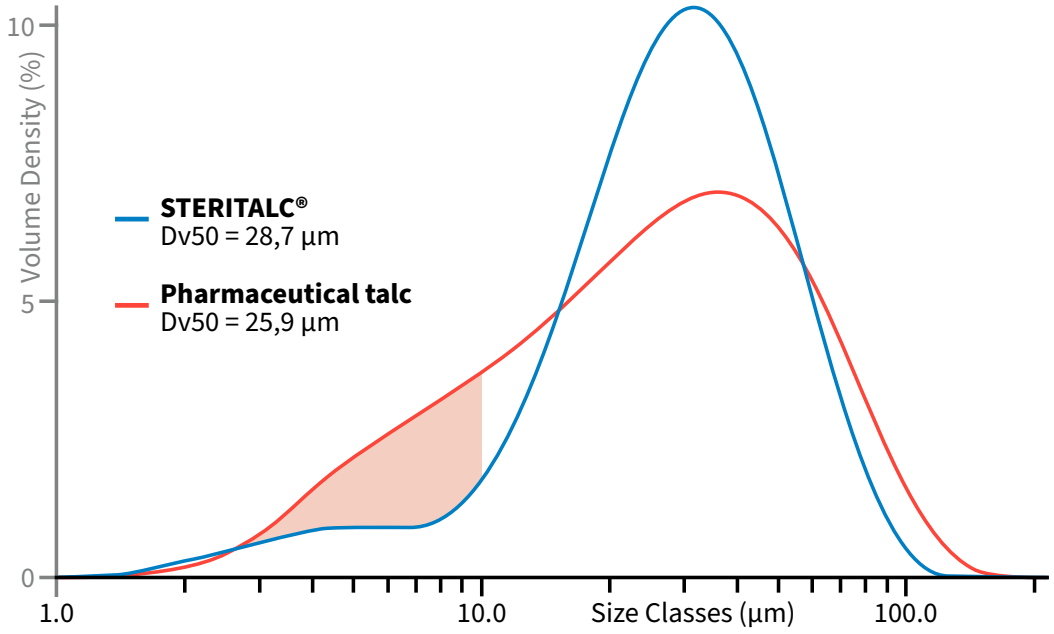
		DV(10)*	Dv(25)*	Dv(50)*	Dv(75)*	Dv(95)*
Test order ID	Required (µm) / Measured (µm)	9.3 – 13.42	15 – 19.82	24.2 – 31	36.5 – 46.2	61.1 – 76.24
REF_TCF0450GGA04 (Talcum SALF 4g)	M†	**6.34**	12.3	**25.5**	45.3	82.6
REF_TCF0250GGA04 (Talcum SALF 2g)	M†	**6.43**	12.5	**25.6**	45.2	84.6
REF_TCF0450GGA04 (Talcum SALF 4g)	M†	**6.61**	12.7	**26.0**	45.6	81.7
REF_TCF0250GGA04 (Talcum SALF 2g)	M†	**6.65**	12.8	**25.9**	45.0	80.4
	Average	**6.51**	12.58	**25.75**	45.28	82.33

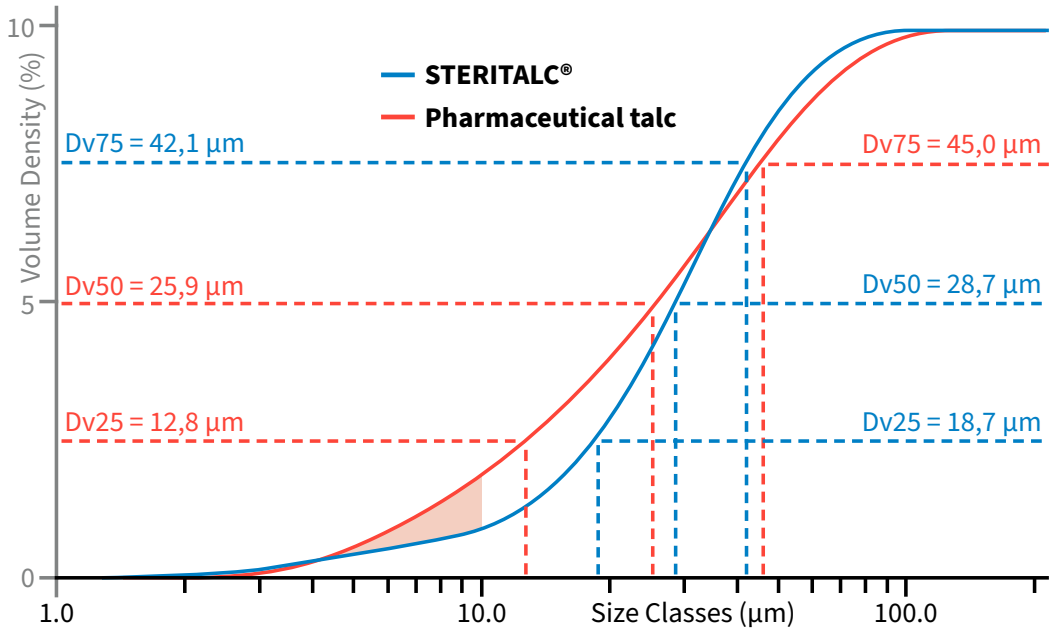
* Dv(x) - the point in the size distribution, up to and including which, x% of the total volume of material in the sample is 'contained'.

† Measured (µm)

Appendix II

Comparison of particle size distribution between STERITALC® and pharmaceutical talc





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As a Senior Trial Manager and Research Governance Manager at the University of Manchester she headed medical research projects including clinical trials as well as governance, and risk compliance across all faculties. Dr. Karen Schafheutle joined bess group as Clinical Affairs Manager in 2022.

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