March 27th, 2018

Summary report

Study on the over-dosing risk of the « ENFit Low Dose Tip » syringe during its use

By Vygon and ANDHEO

Authors :

- Christelle LETOURMY, Principal International Marketing Manager, VYGON
- Tristan SOUBRIE, Associate Director, ANDHEO

Content

1. Context

As written in Annex A of ISO 80369-3: 2016, "Concerns have been raised about the possible risks of delivering inaccurate doses of medicines in certain clinical practices across high risk subpopulations (e.g. neonatal patients) if using a reversed connection system (female to male). [...] Laboratory testing also shows a mid-tolerance E1 [ENFit] connector pair in a female to male orientation displaces a mean average of 0,148 ml (min 0,089 ml and max 0,179 ml with an *n* = 32) of fluid." [1]

In order to respond to this over-dosing risk, a new syringe design called Low Dose Tip (LDT) has been proposed for inclusion in ISO 20695 (EN1615 / EN1618 revision). However, the question is: **does the LDT syringe actually eliminate the over-dosing risks?**

Laboratory tests were carried out and a summary of the results was provided during the CEN/TC205/JWG16 meeting in Brussels in May 2016 [2] : The Low Dose Tip syringe reaches the +/- 10% accuracy level **when used as instructed by the manufacturer**, i.e. ensuring that the liquid contained in the LDT syringe moat is completely removed.

2. Objective of the study

The instructions for use of the LDT syringe differ significantly from the current conventional use of a syringe. An additional step is required after realigning the volume: the LDT syringe must be tapped / flicked / wiped in order to remove the fluid from the moat. This extra step is specific to the LDT syringe, it does not apply to the other syringes on the market.
Therefore, to include this LDT syringe in ISO 20695, we must ensure the safety and the dose accuracy of the design even in case of misuse. Like any new medical device, we must comply with the ISO 14971 requirements by conducting a comprehensive risk assessment.

The objective of the study is: **to know the dose accuracy of the LDT syringe when used according to the current conventional protocol (and not according to the manufacturer's instructions), thus entailing the risk to have liquid contained in the moat.**

3. Observation during benchtop manipulations - by Vygon

a. Context

Bench-top manipulations were performed to visually determine if there was a risk of overdosing when using the LDT syringe according to the current conventional syringe protocol and not according to the manufacturer's instructions.

b. Protocol

Two kinds of sampling were carried out:

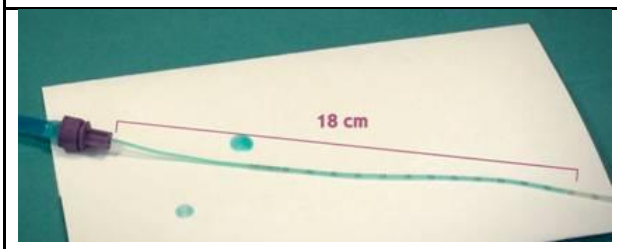
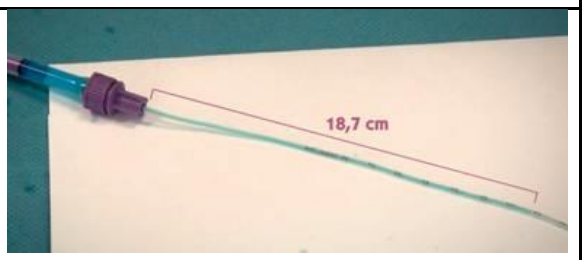
- Cup-filling:
    1. The LDT syringe connector has been dipped directly into the fluid to carry out the sampling
    2. The air bubbles have been removed by tapping the syringe body with the finger. The syringe was held vertically (connector up)
    3. The volume contained in the syringe body has been realigned. The syringe was held vertically (connector up)

4. The LDT syringe has been connected to the ENFit male connector of the feeding tube without pushing the plunger (no injection). The syringe was held horizontally (connector down).

- Sampling straw:
    1. A sampling straw has been connected to the LDT syringe
    2. The straw has been dipped into the liquid to carry out the sampling
    3. The straw has been disconnected after sampling
    4. The air bubbles have been removed by tapping the syringe body with the finger. The syringe was held vertically (connector up)
    5. The volume contained in the syringe body has been realigned. The syringe was held vertically (connector up)
    6. The LDT syringe has been connected to the ENFit male connector of the feeding tube without pushing the plunger (No injection). The syringe was held horizontally (connector down).

c. Results

The visual observation was as follows:

Cup-filling	**Sampling straw**
	

An estimate of the volume transferred to the feeding tube was done using a computer-aided design software called SOLIDWORKS®.

Here is the drawing and the result of the estimate (male ENFit connector + 4Fr feeding tube) :

For the « cup-filling », the displaced volume is estimated at 0,154 ml

For the « sampling straw », the displaced volume is estimated at 0,157 ml

d. Conclusion

These benchtop manipulations have shown that the LDT syringe hub can be filled with liquid if the LDT syringe is used according to the current conventional syringe protocol and that this liquid could be displaced into the feeding tube (risk of overdosing).

However, laboratory tests can unintentionally lead to biases related to the human manipulation (unequal movements, different speed, variable inclination, etc.). These biases can influence the results. This could also explain the results published in Annex A of ISO 80369-3, which show large and

unexplained dispersions of the volume displaced by ENFit: " min 0,089 ml and max 0,179 ml with an n = 32".

Therefore, Vygon decided to deepen the study by carrying out an analysis with a computer-aided design software, called SOLIDWORKS®.

4. CAD evaluation - SOLIDWORKS®- by Vygon

a. Objective

This evaluation consists of determining the theoretical displaced volume when a LDT syringe connects to a male ENFit connector according to the maximum and minimum tolerances of the connectors.

b. Hypothesis

Here, it is considered that a LDT syringe, having been filled according to the current conventional protocol of use, may have a hub fully filled with liquid. The introduction of the male ENFit connector in the LDT syringe hub will therefore displace the liquid (contained in the LDT hub) into the feeding tube. The displaced volume will be the equivalent to the part of the inserted male ENFIT connector in the LDT hub.

c. Protocol

I. Material and Method

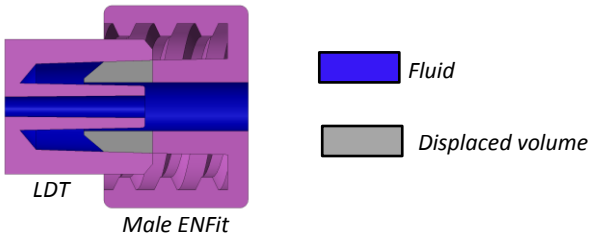
A computer-aided design software called SOLIDWORKS®, edited by Dassault Systèmes, was used.

A 3D modeling of the connectors was carried out under SOLIDWORKS® with the dimensions coming from:

- ISO 80369-3: 2016, for the male ENFit connector
- ISO / DIS 20695, for the LDT syringe.

Adequate functions of SOLIDWORKS® have been applied to calculate the following volumes:

- The dead space is the volume occupied by the fluid inside a connector.
- The displaced volume is the volume occupied by the male connector in the female connector when the cones are in contact, as shown in the example below:



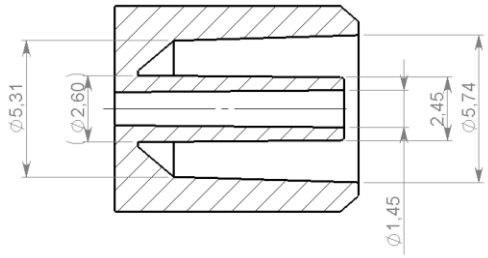
These volumes will be quantified in min / max tolerances via the SOLIDWORKS® CAD modeling.

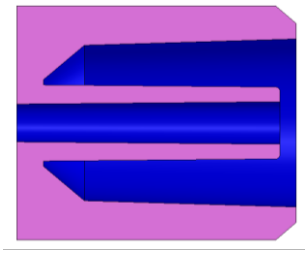
II. Tested configurations & computations

		ISO 80369-3:2016 ***Male ENFit***		***ISO/DIS 20695*** ***LDT syringe***	
		Internal Diameter	Outer Diameter	Internal Diameter	Outer Diameter
Model 1	MAXIMUM dead space	-	-	MAX	*No impact*
Model 2	Minimum dead space	-	-	Min	*No impact*
Model 3	MAXIMUM displaced volume	Min	Min	MAX	*No impact*
Model 4	Minimum displaced volume	MAX	MAX	Min	*No impact*

Model 1 : MAXIMUM dead space of the LDT syringe

Dimensions and CAD model





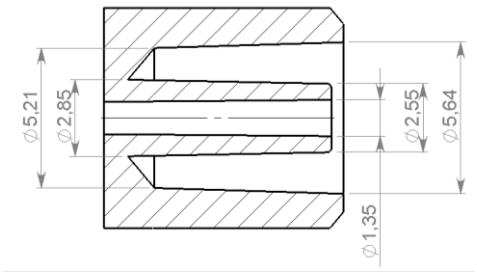
Calculated dead space

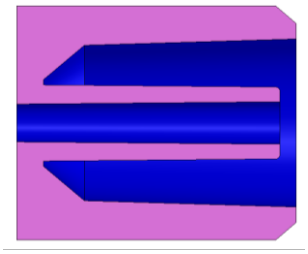
(blue part)

0.162 ml

Model 2 : **Minimum dead space of the LDT syringe**

Dimensions and CAD model





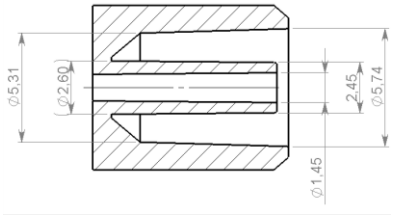
Calculated dead space

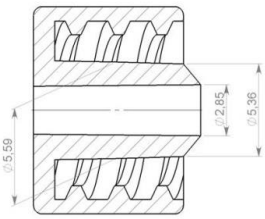
(blue part)

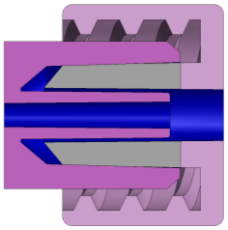
0.143 ml

Model 3 : MAXIMUM volume displacement of the LDT syringe

Dimensions and CAD model







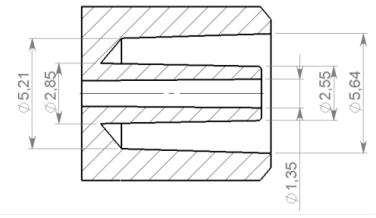
Calculated displaced volume

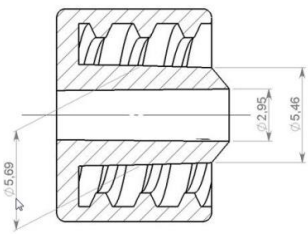
(grey part)

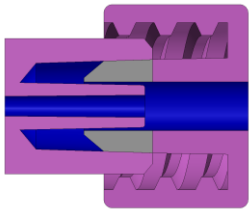
0.120 ml

Model 4 : Minimum volume displacement of the LDT syringe

Dimensions and CAD model







Calculated displaced volume

(grey part)

0.061 ml

d. Results

		LDT syringe
Dead space	*MAXIMUM dead space (ml)*	0.162
	Minimum dead space (ml)	0.143
	Dead space variation (Max-Min) (ml)	0.019
Volume Displacement	*MAXIMUM displaced volume (ml)*	**0.120**
	Minimum displaced volume (ml)	**0.061**
	Displaced volume variation (Max-Min) (ml)	**0.059**

e. Conclusion

This evaluation shows that the part of the inserted male ENFIT connector in the LDT syringe hub can cause a maximum volume displacement (overdosing) of 0.120ml.

However, since the CAD evaluation did not take into account parameters such as gravity or surface tension, Vygon made the decision to initiate a more in-depth study of fluid behavior during connection and to delegate this study to an independent company specialized in the numerical simulation of the fluid dynamics, called ANDHEO.

5. Computational Fluid Dynamics analysis –by ANDHEO

a. Choice of the model

The independent specialist company ANDHEO has been selected because it uses a recent simulation software, called XFlow, developed by the Spanish company NextLimit acquired in 2016 by Dassault Systèmes. XFlow simulates in 3D the displacements of a fluid using the so-called "Lattice-Boltzmann" method, based on the laws of particle behavior (mesoscopic approach) rather than those of the continuous medium (mascroscopic approach). The discretization of the computational domain is then not based on a mesh, which would geometrically rest the solid bodies, but on a network of nodes, which may pass through the bodies. Taking into account the movements of objects and the liquid / air boundaries is greatly facilitated. This tool is therefore the best to deal with this problem of the syringe/feeding tube connection.

b. Model definition and simulation parameters

I. Phase 1 [3]

A first phase of the study consisted in validating the feasibility with several models of connection. Several numerical simulation parameters have been tested and studied but, for simplicity, we will not detail this first phase in this summary report. We will retain the following key results:

- In order to obtain the stability of the computation, a variable spatial resolution (distance between 2 nodes Δx) was not possible; this led to fixing it, either at 40 µm (ie 6.10^6

computational nodes) or at 20 µm (ie 52.10^6 computational nodes) over the entire studied fluid domain.

- While we assumed so far a planar liquid surface; in practice, it is common that the volume contained in the syringe hub leads to the formation of a meniscus - "fluid bubble" - on the surface of the syringe hub, cf. Figure 1.

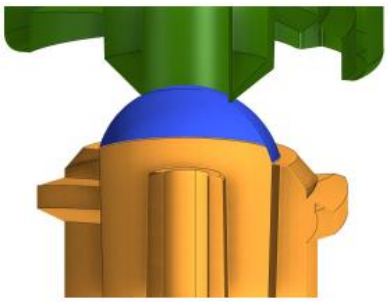


Figure 1. Illustration of a meniscus (blue) on the surface of the LDT syringe hub (yellow)

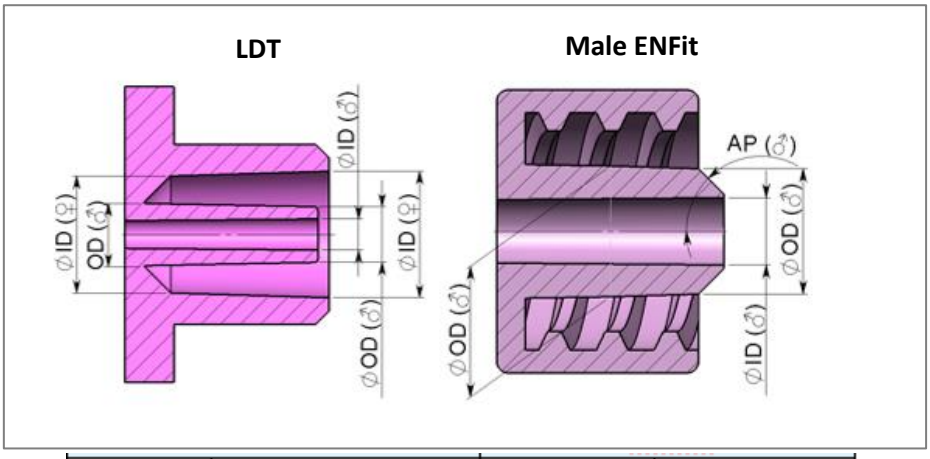
Depending on the size of the meniscus, the displaced volume might change and the behavior of the fluid likewise. This parameter must be taken into account.

II. Phase 2 [4]

The second phase consists in numerically simulating the connection by helical motion, of the LDT connector (syringe) with a male ENFit connector (feeding tube), in the presence of fluid in the LDT connector (proven risk during benchtop manipulations, see §3). The objective is to compute the volume of fluid displaced into the inside tube of the male ENFit connector ("displaced volume") and the volume of fluid expelled into the threads of the male ENFit connector ("leak"), in the presence or absence of a meniscus.

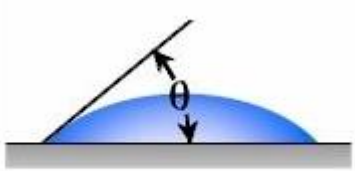
The simulation parameters are as follows:

- The dimensions of the connectors are derived from ISO / DIS 20695 (LDT connector) and ISO 80369-3 (male ENFit connector). The following values have been taken into account:



LDT	ID maxi (♀) OD (♂) mini	**Male ENFit**	OD mini (♂) ID maxi (♂) AP maxi (♂)

- The liquid has the same properties as water at 288,15°K (15°C) :
  - Dynamic viscosity : μ = 0.001 [Pa.s]
  - Density : ρ = 998.3 [kg.m^{-3}]
  - Surface tension : γ = 0.0728 [N.m−1]
  - Contact angle of the liquid on walls: θ = 90 [deg] or 30 [deg]
- The gravity is always applied at an angle of 45 °, which is typical clinical use.
- The male ENFit connector has a rotational speed of 30RPM. The LDT connector is fixed.



To better understand the influence of the various involved parameters, six computations were conducted.

c. Computations

The details of the cases are given in Table 1 below:

Case	Δx	Δt	t_f	θ	Model	Free surface initial condition
1	40 $[\mu m]$	4.0×10^{-6} $[s]$	0.84 $[s]$	90 $[deg]$	Free Surface	Flat
2	40 $[\mu m]$	4.0×10^{-6} $[s]$	0.10 $[s]$	30 $[deg]$	Free Surface	Flat
3	40 $[\mu m]$	4.0×10^{-6} $[s]$	0.20 $[s]$	30 $[deg]$	Free Surface	Meniscus $\delta = 0.25$ $[mm]$
4	40 $[\mu m]$	4.0×10^{-6} $[s]$	0.20 $[s]$	90 $[deg]$	Free Surface	Meniscus $\delta = 2.15$ $[mm]$
5	20 $[\mu m]$	2.5×10^{-6} $[s]$	0.10 $[s]$	90 $[deg]$	Free Surface	Flat
6	40 $[\mu m]$	2.5×10^{-6} $[s]$	0.50 $[s]$	90 $[deg]$	Phase Field	Flat

Table 1. Summary of the computations – Δx : spatial resolution, Δt : time increment, tf : total time of the simulation , θ : contact angle and δ : height of the meniscus

The cases 1, 2, 3 and 4 aim at identifying the effects on the fluid dynamics of the contact angle and of the presence of a meniscus. The contact angle determines the wettability of a surface, it basically measures how spherical (large contact angle) or ellipsoidal (small contact angle) a bubble would be when resting on a given surface. In this study, extreme values have been chosen to highlight the sensitivity of the results to this parameter, therefore, contact angles of θ = 30 and 90 [deg] have been considered.
Only the "case 1" is carried out to completion (total screwing of the male ENFit connector on the LDT syringe connector), ie tf = 0.84 s, because the fluid reaches a virtually constant displacement from tf = 0.10 s for “free-surface” models. For the cases 3 and 4, the simulation times were tf = 0.20 s to ensure that the entire meniscus was passed.

The "case 5" aims at confirming the results obtained with the basic parameters by refining the spatial resolution (Δx), twice lower in each direction, ie 20 µm. This is a standard methodology to validate a model. The number of nodes in the network is then increased by 8, from 6 to 52 million. The numerical stability being guaranteed by a ratio between the spatial resolution (Δx) and the time increment (Δt), the latter (Δt) was divided by about 2 to maintain the same level of stability.

The "case 6" involves a specific model of surface simulation, called "Phase field". This model takes into account the two fluids present on both sides of the interface - air and water - and automatically refines the node network at the interface to properly determine its position. It is more advanced than the "Free surface" model used so far. Indeed, this "Free surface" model considers only the liquid

and does not take into account the influence of the air on it to determine the position and the shape of the interface.
Due to the automatic space refinement, the time step had to be reduced compared to the “free surface” model to maintain a satisfactory numerical stability. The chosen simulation time was longer (tf = 0.50 s) in order to bring the comparison with the "Free surface" model with a significant time.

For each "case", the period required by the computation is about 10 calendar days - 60 days in total.

d. Results

The different results obtained with the cases listed above are provided in Table 2 below.

Case	Leak	Meniscus	Total displaced volume
1	$0.0\ [mL]$	$0.0\ [mL]$	$0.120\ [mL]$
2	$0.0\ [mL]$	$0.0\ [mL]$	$0.120\ [mL]$
3	$0.0\ [mL]$	$2.3 \times 10^{-3}\ [mL]$	$0.122\ [mL]$
4	$0.0\ [mL]$	$3.3 \times 10^{-2}\ [mL]$	$0.153\ [mL]$
5	$0.0\ [mL]$	$0.0\ [mL]$	$0.120\ [mL]$
6	$0.0\ [mL]$	$0.0\ [mL]$	$0.120\ [mL]$

Table 2. Summary of the results – « Leak » : liquid expelled into the threads of the male ENFit connector and "Total displaced volume" : liquid displaced into the inside tube of the male ENFit connector

The results show that there is no leakage into the threads of the male ENFit connector during connection and that the entire volume is displaced into the inside tube of the male ENFit connector (feeding tube).

Then, the values of the total displaced volumes in the absence of meniscus are exactly equal to those obtained by CAD simulation (see § 4. CAD evaluation - Solidworks).

The results of Case 6 ("Phase Field") are identical to the results of Case 1. Therefore, the basic "Free surface" model can be considered relevant.

The results of Cases 5 and 1 are identical. Therefore, the spatial resolution of 40µm is sufficient.

The results of Cases 1 and 2 are identical. This implies that the contact angle has no influence on the displaced volume.

When a meniscus is present (Cases 3 and 4), its volume is entirely displaced into the inside tube of the male ENFit connector (feeding tube) and induces a variability of the displaced volume, which can explain the variability observed during the benchtop manipulations.

In none of the cases, it was observed that liquid was expelled into the threads of the male ENFit connector. Even when there is a meniscus, the software predicts that the surface tension prevents the rupture of the liquid interface, forcing the liquid to be immediately sucked into the male ENFit connector (feeding tube). From there, the smaller the free-surface, the greater the surface tension effect and the lower the possibility of "leakage" to the outside. This confirms the relevance of the shortened simulation times chosen for Cases 2 to 6.

6. Conclusion

The displaced volume of the LDT syringe is 0.120ml in case of presence of liquid in its hub and can be increased to 0.153ml in case of presence of a meniscus. In addition, no leakage is observed in the threads of the male ENFit connector (feeding tube) during connection. The "displaced volume" is therefore an over-dosing that occurs unintentionally during the connection

The basic simulation, which involves surface tension and gravity, has been doubly confirmed on the one hand with a twice higher degree of spatial accuracy and on the other hand with a more advanced liquid / air interface model. These last computations confirmed the robustness of the basic parameters used.

Although we have varied the liquid / solid contact angle and considered the presence of meniscus of variable volume, the overall results confirm that there is no "leakage" of liquid to the threads of the male ENFit connector. In all configurations, all the liquid is displaced into the feeding tube. We can therefore reasonably conclude that at this scale, the effects of surface tension take precedence over other parameters and "avoid" liquid ejection to the outside (threads).

6. General conclusion

Preliminary benchtop manipulations revealed that overdosing was possible with the Low Dose Tip syringe if fluid was present in the hub.

This is why a CAD evaluation was subsequently carried out to determine what the overdosing could theoretically be administered during the connection. Computations have shown that the part of the male ENFit connector (feeding tube) inserted in the LDT syringe hub can cause a volume displacement of 0.120ml maximum. However, this CAD evaluation does not take into account the physical parameters (gravity, surface tension, viscosity ...) that can influence the result.

A numerical simulation of fluid dynamics, taking into account gravity, surface tension, connection speed, fluid surface and other parameters, was therefore conducted by an independent specialized company (ANDHEO). The results confirmed that:

- An over-dosage of 0.120ml could be administered in case of presence of liquid in the LDT connector.
- This over-dosage can be increased to 0.153ml if a meniscus is present.
- No "leakage" of liquid into the threads of the male ENFit connector is made, the surface tension effect is extremely high and induces an immediate suction in the inside tube of the male ENFit connector. In all configurations, all the liquid is displaced into the feeding tube.
- The results of the CAD evaluation by Solidworks are confirmed and can be considered as representative of a numerical simulation, if the liquid surface is flat (absence of meniscus).

Therefore, the LDT syringe does not eliminate the risk of over-dosing. A risk of over-dosing persists and corresponds to 0.120ml, equivalent to the over-dosage of the standard ENFit syringe according to a CAD evaluation under Solidworks [5].

7. References

[1] NF EN ISO 80369-3 : 2016 - Small-bore connectors for liquids and gases in healthcare applications — Part 3: Connectors for enteral applications.

[2] CEN-TC205-WG16_N0032_Low_Dose_Tip-Presentation

[3] M. Biason, PhD T. Soubrié : *TECHNICAL REPORT n° dh-16-06_rt-01-v05 – Connection for enteral administration*, Andheo, 2016/09/09.

[4] PhD C. Turquand d'Auzay, PhD T. Soubrié : *TECHNICAL REPORT n° dh-16-34_rt-01-v02 – Connexion for enteral administration*, Andheo, 2017/02/07.

[5] Dead space and displaced volume of ISO 80369-3:2016 [ENFit] connector by Solidworks, Vygon, February 2018