	FLEXMAG 4050 C - VALIDATION GUIDE	Rev.04

Prepared by	Revision number	Date of modification	comments
Christine Perfetti	R00	06/12/2018	
Christine Perfetti	R01	05/03/2019	Autoclave
Christine Perfetti	R02	18/06/2019	Pouches
Christine Perfetti	R03	21/01/2021	Electrodes
Christine Perfetti	R04	21/03/2022	English wording

Table of Content

1. Introduction

After 60+ years of experience in Electromagnetic flow measurement, KROHNE developed a cutting-edge innovation dedicated to the demanding biopharma market.
With the FLEXMAG 4050 C we introduce the most accurate flowmeter on the market with a disposable tube.

This validation guide introduces a non-exhaustive list of tests and certificates that composes the validation package of the FLEXMAG 4050 C and provides examples of test results. It details the physical, functional, chemical and biological tests and compliance.

The FLEXMAG 4050 C's performances are maintained under the conditions of the application: The accuracy and integrity are maintained after gamma irradiation, under pressure, during the shelf life, …

The wetted part complies with the biological and chemical requirements for the raw material and finished parts post irradiation.

2. Presentation FLEXMAG 4050 C

The FLEXMAG 4050 C is the first electromagnetic flowmeter that features a disposable flow tube designed specifically for single use biopharmaceutical applications. It is made of two parts: the transmitter that includes the magnetic field circuitry and electronics, and the single use tube which is in contact with the media.

3 transmitter sizes can accommodate with 5 flow tube sizes as indicated in the table:

Transmitter	Tube size
Small transmitter	¼"
Medium transmitter	3/8" and ½"
Large transmitter	3/4" and 1"

The FLEXMAG 4050 C provides a completely stable, direct and accurate volumetric flow measurement, unaffected by fluid properties such as color or density.

3. Regulatory Agreement

3.1. ISO 9001-14001

The FLEXMAG 4050 C is manufactured in a KROHNE manufacturing site which is registered to ISO 9001 and ISO 14001.

3.2. ISO 13485

The wetted part of the FLEXMAG 4050 C is manufactured in a ISO 13485 certified site. The cleanroom for manufacturing and packaging conforms to ISO14644-1 class 7.

3.3. FDA CFR Part 177

The polymer Udel P-1700 NT 11 that composes the wetted part of the FLEXMAG 4050 C complies with Title 21 Part 177.1655 promulgated under the Federal Food, Drug and Cosmetic Act.

3.4. CE marking

The FLEXMAG 4050 C complies with the protection requirements defined in the European Council directives:

3.4.1. EMC

The European Directive 2014/30/EU regulates the electromagnetic compatibility of equipment. The FLEXMAG 4050 C fulfils the harmonized standard EN 61326-1:

- Emission EN 61326-1 (2013) Class B,
- Immunity EN 61326-1 (2013) Industrial

3.4.2. Low voltage directive

The safety requirements according to the Low Voltage Directive 2014/35/EU are assessed according to the general safety requirements of IEC 61010-1: 2010, which the FLEXMAG 4050 C complies with.

3.4.3. RoHS

The FLEXMAG 4050 C complies with the directive 2011/65/EU including delegated directive (EU) 2015/863 Annex III, by decision N° 768/2008/EC of the European Parliament and of the Council of 8 June 2011.

3.5. REACH

On June 1st, 2007 the Regulation (EC) N°. 1907/2006 of the European Parliament and of Council concerning the registration, evaluation, authorization and restriction of chemical substances (REACH) came into effect.

KROHNE aims to ensure a high level of protection of human health and the environment.

KROHNE is supplying only non-chemical products (articles). These articles, including the disposable flow tube used in the FLEXMAG 4050 C, their packaging materials, do not contain any substances which are intended to be released under normal or reasonably foreseeable conditions of use. Therefore, a registration according Article 7(1) does not apply.

On part of our suppliers there is no restriction for the ability to deliver.

3.6. BSE/TSE free

The disposable flow tube used in the FLEXMAG 4050 C is not manufactured from any type of material originating from animal products or derivatives of such products. The flow tube is not exposed to any material of ruminant origin during its manufacturing.

The FLEXMAG tube does not constitute a risk of transmission of Bovine Spongiform Encephalopathy (BSE) or Transmissible Spongiform Encephalopathy (TSE).

4. Biological Compatibility

The FLEXMAG tube that constitutes the wetted part of the flowmeter, is made of polysulfone Udel P-1700 NT 11. The electrodes of Hastelloy C22.

4.1. ISO 10993

ISO 10993 testing has been completed for Udel P-1700 NT 11, as follows.

- ISO 10993:5 Cytotoxicity
- ISO 10993:10 Maximum sensitization and intracutaneous reactivity with sodium chloride and sesame oil extracts
- ISO 10993:11 Systemic toxicity study with sodium chloride and sesame oil extracts
- ISO 10993:18 Physico-chemical testing with water and isopropyl alcohol extracts

4.2. USP VI

The polymer used for the manufacturing of the tubes in contact with the media is USP VI compliant.

The tube manufactured and irradiated at 25-40 kGy was tested in a laboratory. The study was based on the following references USP <88> Biological Reactivity Tests, in Vivo and ISO/IEC 17025, 2005 (competences for testing and calibration laboratories).

The USP 0.9% NaCl, CSO, 1 in 20EtOH and PEG extracts of the gamma irradiated tube did not produce biological response following:

- Intracutaneous Injection in rabbits
- Systemic Injection in mice
- Implantation in rabbits

Based on the criteria of the protocol and the USP guidelines for class VI Plastics – 70°C, the FLEXMAG tube, gamma irradiated, meets the requirement of the tests and is USP Class VI compliant.

4.3. USP <87> Cytotoxicity- Biological Reactivity Tests, in Vitro

The tube manufactured and irradiated at 25-40 kGy was tested in a laboratory. Based on the USP <87> guidelines, the FLEXMAG tube, gamma irradiated, meets the requirement of the tests and is not considered to have a cytotoxic potential.

4.4. Hemolysis

Hemolysis testing has been completed for Udel P-1700 NT 11, based on the IOS: Biological Evaluation of Medical Devices, Part 4: Selection of Tests for Interaction with Blood. The mean hemolytic index was 0%. The Udel P-1700 NT 11 is nonhemolytic.

4.5. Bacterial Endotoxin

The FLEXMAG tube trial method is validated for the bacterial endotoxin test by the kinetic colorimetric technique in accordance with the specifications of the European Pharmacopoeia 9th edition (2017/01)-chapter 2.6.14.

The FLEXMAG tube was tested and conforms to the targeted parameters, with an Endotoxin limit ≤ 0.05 UI/ml.

5. Chemical compatibility

5.1. USP <661> Physico-chemical tests

The tube manufactured and irradiated at 25-40 kGy was tested in a laboratory. The study was based on the following references USP <661>, section “Physicochemical tests”, involving Aqueous extracts, Hexane and Ethanol. Nonvolatile residue, residues on ignition, heavy metals, buffering capacity were analyzed and meet the criteria.

The FLEXMAG tube, gamma irradiated, complies with the requirements of USP <661>, section “Physicochemical tests”.

5.2. Extractables study

The tube manufactured and irradiated at 25-40 kGy was tested in a laboratory according the following extraction method: Dynamic extraction by circulation 24h and 40°C using 3 extraction solvents: with UPW, adjusted to pH2, adjusted to pH10, with 50% Ethanol in UPW.

The Extractable study is available under payment.

5.3. Specific Chemical substances

5.3.1 Bisphenol A

The Bisphenol A is used in the manufacture of the polysulfone. However, it is consumed in the polymerization process. There is a trace amount of unreacted Bisphenol A monomer left behind in the polymer.

Bisphenol A is listed in the California Prop. 65, which lists chemicals known to cause cancer, birth defects, or reproductive harm.

5.3.2 Phtalates

Phtalates are not expected to be present in the Udel P-1700 NT 11.

6 Functional tests and compliance

6.1. Particulate matters

The FLEXMAG tube trial method is validated for the evaluation of the presence of particulates on the product, according the standards:

- European Pharmacopoeia 9th edition (2017/01)-chapter 2.6.19
- USP <788> Particulate matters in injection – Method 1

The FLEXMAG tube conforms to the targeted parameters with particulate limit ≤ 25 /ml.

6.2. Accuracy

The measuring error of the FLEXMAG 4050 C is **below 1 %+/- 1 mm/s** of the measured value. This means that the deviation from the actual measured value is below 1%, except at very low flow due to the noise influence 1 mm/s. This performance remains with each tube changed during the life of the transmitter.

Uncertainty per flow (l/min) per diameter				
Uncertainty	3%	2%	1%	1%
1/4"	0,10	0,2	1,0	3
3/8"	0,21	0,4	1,3	14
1/2"	0,38	0,8	2,2	20
3/4"	0,75	1,7	5,1	62
1"	1,52	3,0	9,1	75

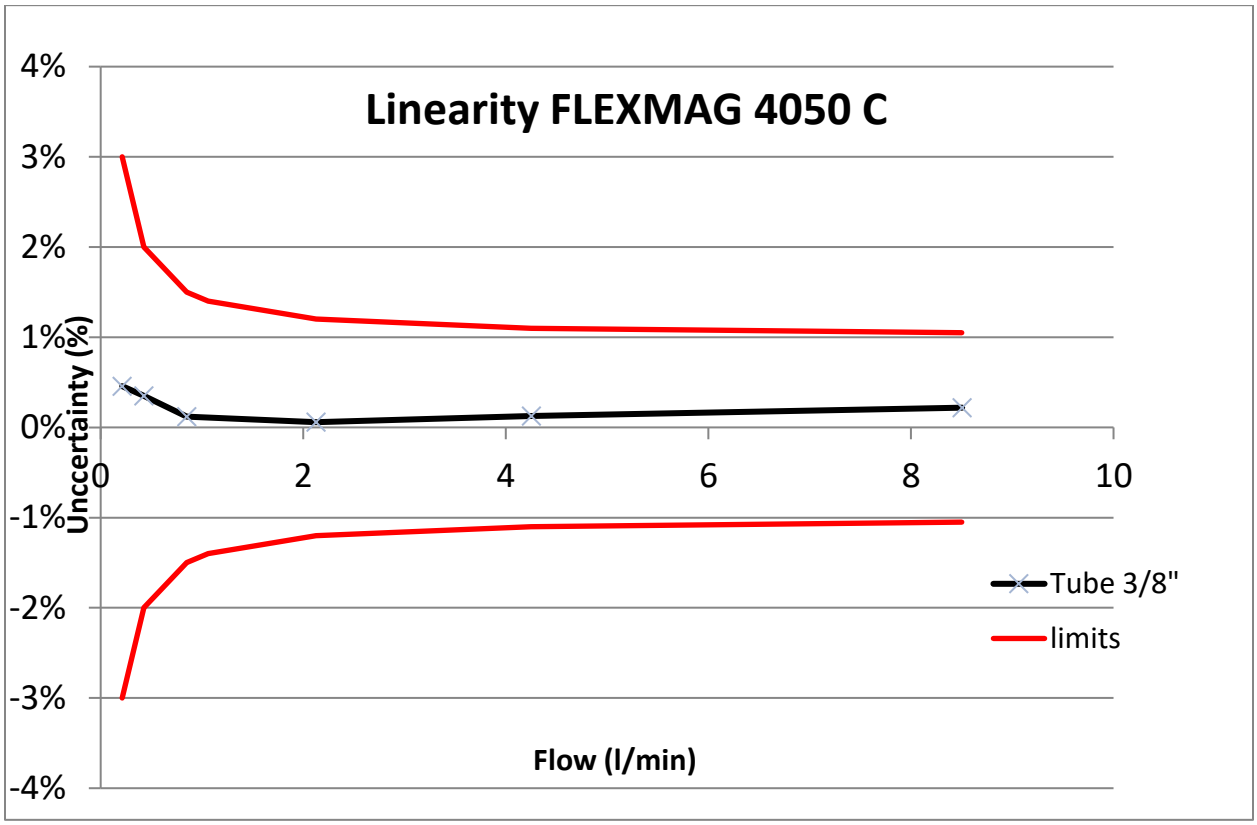

Figure 1: FLEXMAG 4050 C Accuracy

6.3. Influence of pressure

The FLEXMAG tubes are designed to be compatible with the usual pressures of the biopharmaceutical application, up to 4 bar. Qualification tests are made at different pressure values. They confirm that variation of pressures does not affect the accuracy of the FLEXMAG 4050 C, which remains below 1 %+/- 1 mm/s of the measured value.

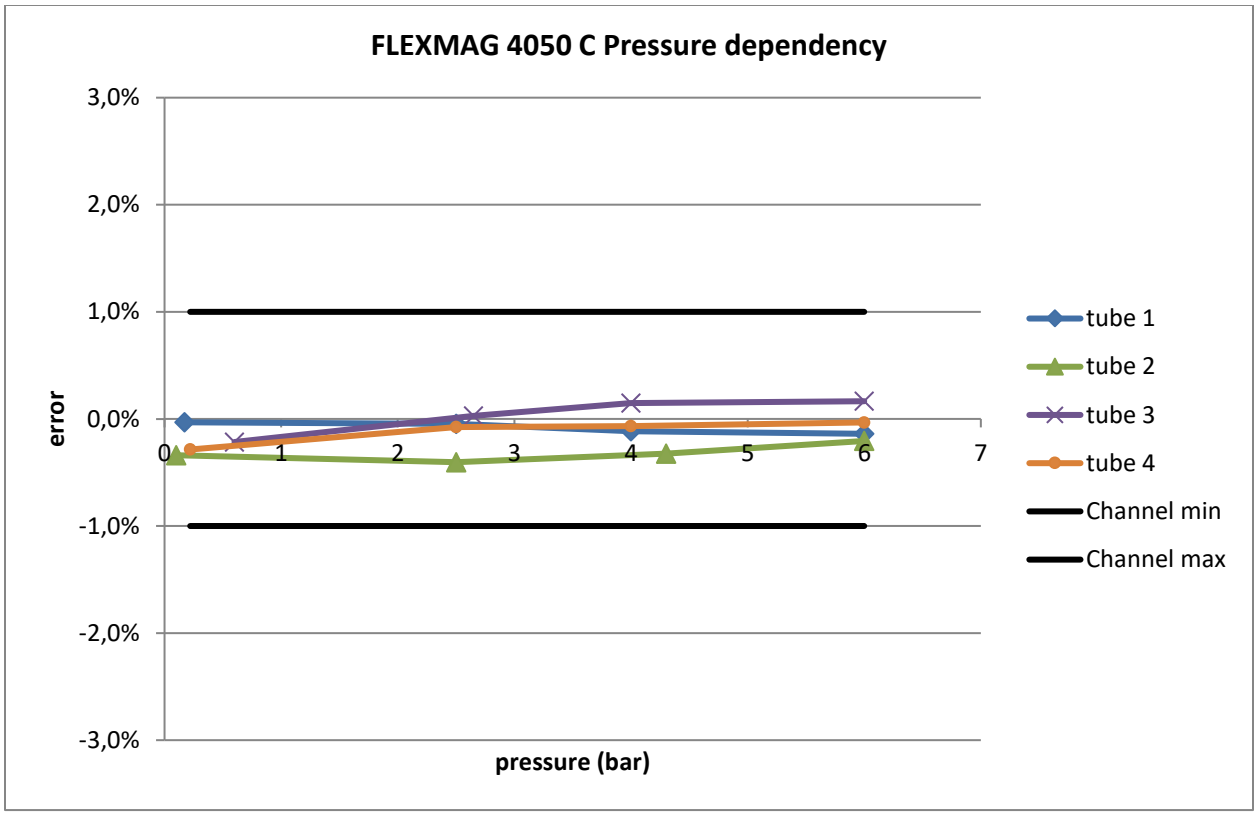

Figure 2: Accuracy with pressure variation

6.4. Influence of temperature

The FLEXMAG tubes are designed for process temperature up to 45°C. Qualification tests confirm that the temperature variations do not affect the accuracy of the FLEXMAG 4050 C, which remains below 1 %+/- 1 mm/s of the measured value.

6.5. Integrity

The integrity of the flowmeter is considered from the design stage, such as the thickness of the tube and the electrodes shape. The integrity is confirmed by testing the tubes in different situations:

- Manufactured tube
- Irradiated tube up to 50 kGy
- Aged tube at 3 years

6.5.1. Burst pressure

The burst pressure of the tube is > 20bar.

6.5.2. Helium test

A stringent acceptance criteria is chosen: 10^{-5} mbar l/s (corresponding to 1 cm^3 gas leakage per day). The integrity of the tube is maintained in all situations.

6.5.3. *Connection with hoses*

The connections of the tube are designed for connecting flexible hoses of the same diameters as the tube itself. The single barb shape design ensures a good contact with the hoses. The flexible hose is inserted up to a stopper ring. The length between the ring and the single barb allows the positioning of closing clamps. This tube design ensures a correct mounting with hoses and integrity, which is confirmed by tests up to 10 bar.

6.6. Influence of sterilization

6.6.1. *Gamma irradiation*

The tubes can be Gamma irradiated at 50 kGy. After irradiation, the performance is not affected and the integrity is maintained.

The measuring error of the FLEXMAG 4050 C remains below 1 %+/- 1 mm/s of the measured value.

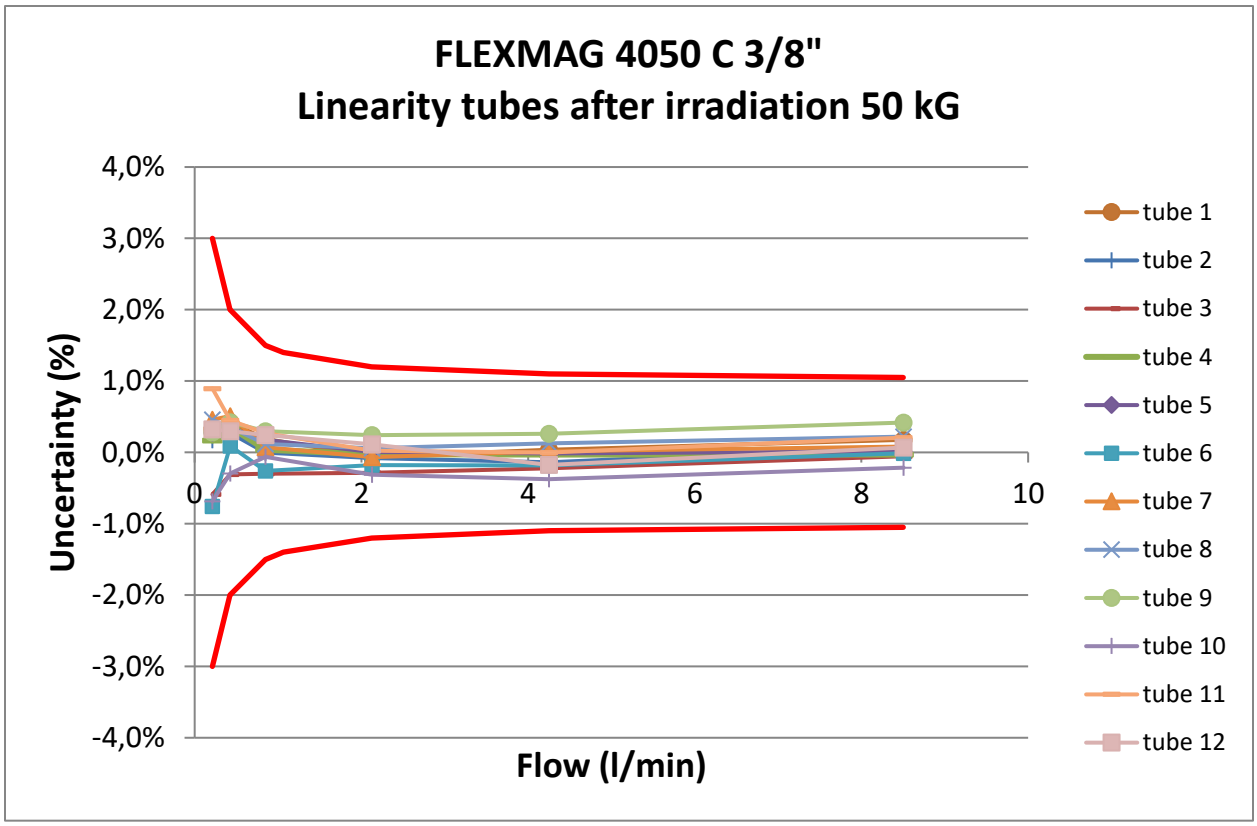

Figure 3: Accuracy after Gamma irradiation

The pouchs PA/PE can be gamma irradiated up to 50 kGy, however the validation of sterilisation is not part of the scope.

6.6.2. *Autoclaving*

The performance is maintained after autoclave at 121°C, 30 minutes.

6.7. Influence of ageing

The shelf life of the tube is 3 years. During this period the performance of the FLEXMAG 4050 C is not affected. The ageing of the tube is accelerated in an oven at 58°C for 3 months, according to the standards:

- EN ISO 11 607: Packaging for terminally sterilized medical devices
- ASTM F 1980 – 07: Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices

The FLEXMAG 4050 C's accuracy remains below 1 %+/- 1 mm/s of the measured value and the integrity tests are confirmed after the ageing period, which confirms the 3 years shelf life.

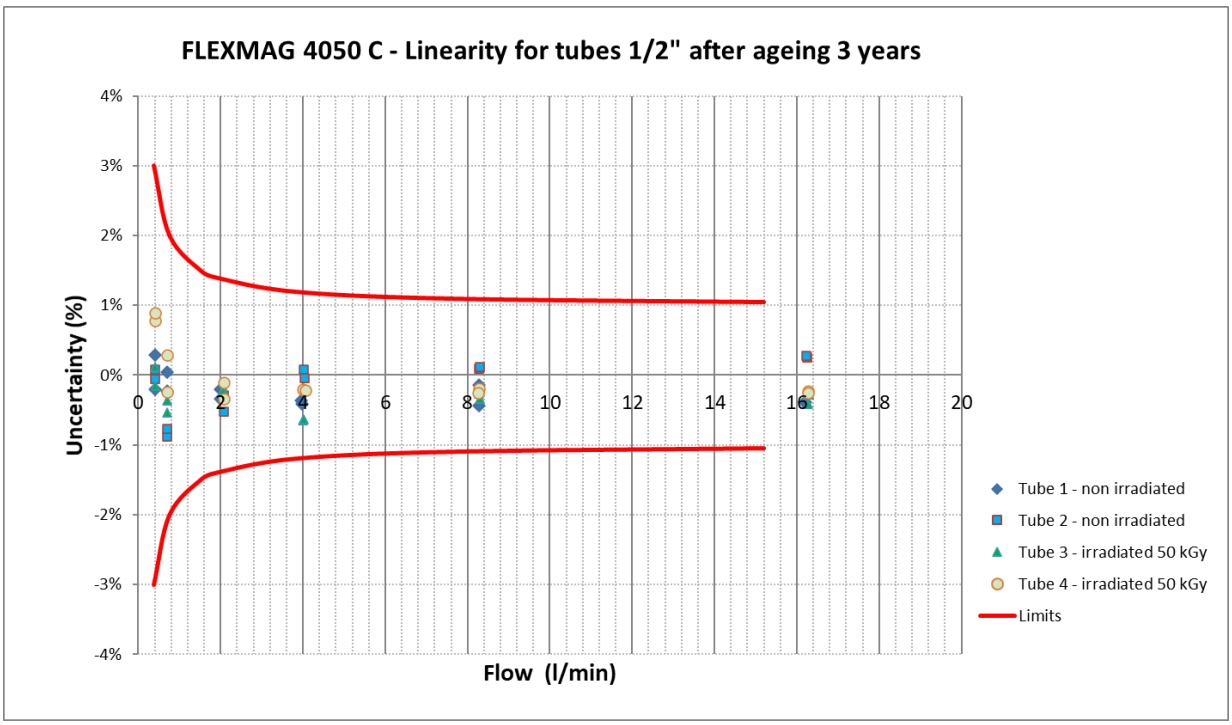

Figure 4: Accuracy after 3 years shelf life

6.8. Pressure loss

The full-bore design of the flow tubes ensures a negligible pressure drop.

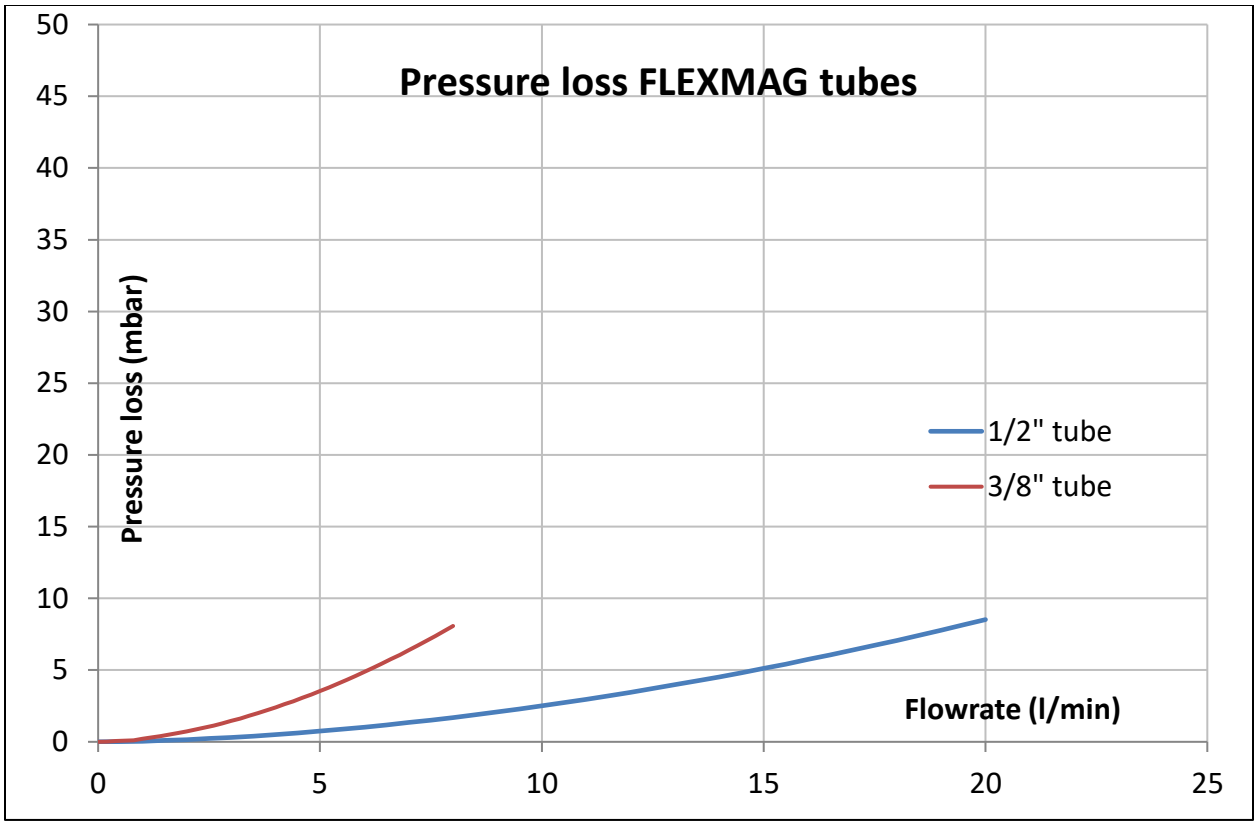

Figure 5: Pressure drop of tube

6.9. Ingress Protection

The FLEXMAG 4050 C complies with the IP54 requirement as defined in standard EN60529.

6.10. Vibration

The FLEXMAG 4050 C was tested for resistance to mechanical stress, by applying vibrations and shocks.

The sine vibration test (general application) was conducted in accordance to the standard IEC 60721-3-4 Class 3M3 and the method IEC 60068-2-6. The flowmeter complies.

The mechanical shock test was conducted in accordance with the standard IEC 60721-3-4 Class 3M5 and the method IEC 60068-2-27.

The FLEXMAG 4050 C passed the tests.

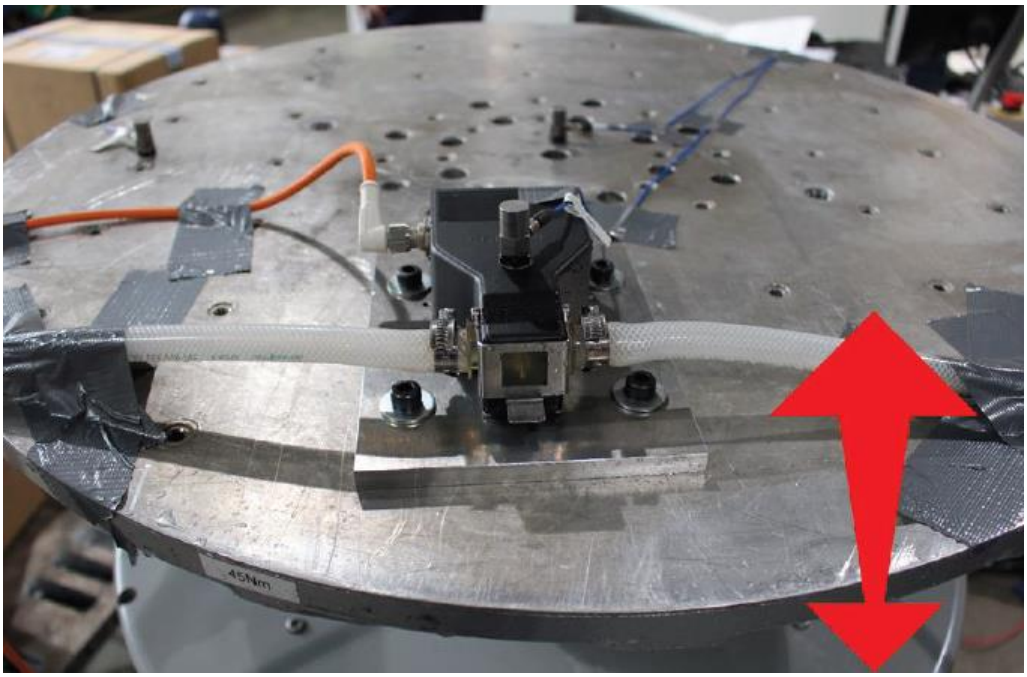

Figure 5: Photo a vibration table, here FLEXMAG mounted in Z direction.

6.11. Shipping tests

The packaging is validated by applying tests based on ISTA 3A, packaged products for parcel delivery shipment, 70kg or less and environmental classification 2M2. The shock test is conducted in accordance to the standard IEC60721-3-2.

The packaging undergoes mechanical stress by applying random vibrations, shocks and drop tests, representing over the road Trailer Spectrum, pick-up and Delivery Vehicle Spectrum, stationary Vibration.

The packed transmitters and the packed tubes passed the tests' requirements.