Cardiovascular implants — Cardiac valve prostheses —

Part 3:
Heart valve substitutes implanted by transcatheter techniques

Implants cardiovasculaires — Prothèses valvulaires —
Partie 3: Valves cardiaques de substitution implantées par des techniques transcathété
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ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 5840-3 was prepared by Technical Committee ISO/TC 150, Implants for surgery, Subcommittee SC 2, Cardiovascular implants and extracorporeal systems.

ISO 5840 consists of the following parts, under the general title Cardiovascular implants — Cardiac valve prostheses:

— Part 3: Heart valve substitutes implanted by minimally invasive techniques
Introduction

No heart valve substitute is ideal. Therefore, a group of engineers, scientists and clinicians well aware of the problems associated with heart valve substitutes and their development has prepared this part of ISO 5840. In several areas, the provisions of this part of ISO 5840 have been deliberately left partially defined so as not to inhibit development and innovation. This part of ISO 5840 specifies types of tests, test methods and requirements for test apparatus. It requires documentation of test methods and results. This part of ISO 5840 deals with those areas that will ensure adequate mitigation of device-associated risks for patients and other users of the device, facilitate quality assurance, aid the cardiac surgeon and cardiologist in choosing a heart valve substitute, and ensure that the device will be presented in a convenient form. This part of ISO 5840 emphasizes the need to specify types of in vitro testing, preclinical in vivo and clinical evaluations as well as to report all in vitro, preclinical in vivo and clinical evaluations. It describes the labels and packaging of the device. Such a process involving in vitro, preclinical in vivo and clinical evaluations is intended to clarify the required procedures prior to market release and to enable prompt identification and management of any subsequent problems.

With regard to in vitro testing and reporting, apart from basic material testing for mechanical, physical, chemical and biocompatibility characteristics, this part of ISO 5840 also covers important hydrodynamic and durability characteristics of transcatheter heart valve substitutes and their delivery systems. This part of ISO 5840 does not specify exact test methods for hydrodynamic and durability testing but it offers guidelines for the test apparatus.

This part of ISO 5840 should be revised, updated and amended as knowledge and techniques in heart valve substitute technology improve.

This part of ISO 5840 is to be used in conjunction with ISO 5840:2005, which will be replaced by ISO 5840-1 in future.
Cardiovascular implants — Cardiac valve prostheses —

Part 3: Heart valve substitutes implanted by transcatheter techniques

1 Scope

This part of ISO 5840 outlines an approach for verifying/validating the design and manufacture of a transcatheter heart valve substitute through risk management. The selection of appropriate verification/validation tests and methods are to be derived from the risk assessment. The tests may include those to assess the physical, chemical, biological and mechanical properties of heart valve substitutes and of their materials and components. The tests can also include those for preclinical in vivo evaluation and clinical evaluation of the finished heart valve substitute.

This part of ISO 5840 defines operational conditions and performance requirements for transcatheter heart valve substitutes where adequate scientific and/or clinical evidence exists for their justification.

This part of ISO 5840 is applicable to all devices intended for implantation in human hearts as a transcatheter heart valve substitute.

This part of ISO 5840 is applicable to both newly developed and modified transcatheter heart valve substitutes and to the accessory devices, packaging and labelling required for their implantation and for determining the appropriate size of heart valve substitute to be implanted.

This part of ISO 5840 excludes heart valve substitutes designed for implantation in artificial hearts or heart assist devices.

This part of ISO 5840 excludes valve-in-valve configurations and homografts.

This part of ISO 5840 does not specifically address non-traditional surgically implanted heart valve substitutes (e.g. sutureless). For these devices, the requirements of both this part of ISO 5840 and ISO 5840:2005 might be relevant and can be considered.

NOTE A rationale for the provisions of this part of ISO 5840 is given in Annex A.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 10993-1, Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process

ISO 10993-2, Biological evaluation of medical devices — Part 2: Animal welfare requirements

ISO 11135-1, Sterilization of health care products — Ethylene oxide — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

NOTE Additional definitions can be found in the informative annexes.
3.1 **accessories**  
device-specific tools that are required to assist in the implantation of the transcatheter heart valve substitute

3.2 **adverse event**  
**AE**  
untoward medical occurrence in a study subject which does not necessarily have to have a causal relationship with study treatment

Note 1 to entry: An AE can be an unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease, temporary or permanent, whether or not related to the prosthetic valve implantation or procedure.

3.3 **arterial end diastolic pressure**  
minimum value of the arterial pressure during diastole

3.4 **arterial peak systolic pressure**  
maximum value of the arterial pressure during systole

3.5 **back pressure**  
differential pressure applied across the valve during the closed phase

3.6 **body surface area**  
$A_{bs}$  
total surface area ($m^2$) of the human body

Note 1 to entry: This can be calculated (Mosteller's formula) as the square root of product of the weight in kg times the height in cm divided by 3 600 (see Reference[12]).

3.7 **cardiac index**  
cardiac output ($CO, l/min$) divided by the body surface area ($A_{bs}, m^2$), in units $l/min/m^2$

3.8 **closing volume**  
portion of the regurgitant volume that is associated with the dynamics of the valve closure during a single cycle

Note 1 to entry: See Figure 1.
Key
X  time
Y  flowrate
1  closing volume
2  leakage volume

Figure 1 — Schematic representation of flow waveform and regurgitant volumes for one cycle

3.9 coating
thin-film material that is applied to an element of a heart valve substitute to modify its physical or chemical properties

3.10 compliance
relationship between change in diameter and change in pressure of a deformable tubular structure (e.g. valve annulus, aorta, conduit), defined in this part of ISO 5840 as

\[ C = 100\% \times \frac{(r_2 - r_1) \times 100}{r_1 \times (p_2 - p_1)} \]

where

- \( C \) is the compliance in units of % radial change/100 mmHg;
- \( p_1 \) is the diastolic pressure, in mmHg;
- \( p_2 \) is the systolic pressure, in mmHg;
- \( r_1 \) is the inner radius at \( p_1 \), in millimetres;
- \( r_2 \) is the inner radius at \( p_2 \), in millimetres.

Note 1 to entry: See ISO 25539-1.
3.11 component-joining material
material, such as a suture, adhesive or welding compound, used to assemble the components of a heart valve substitute, thereby becoming part of the implant device

Note 1 to entry: See examples in Annex B.

3.12 cycle
one complete sequence in the action of a heart valve substitute under pulsatile flow conditions

3.13 cycle rate
number of complete cycles per unit of time, usually expressed as cycles per minute (cycles/min)

3.14 delivery approach
anatomical access used to deliver the implant to the implant site (e.g. transfemoral, transapical, transeptal)

3.15 delivery system
catheter or other device-based system used to deliver the implant to the implant site

3.16 deployed valve diameter
outer diameter (mm) of the implantable device when deployed within the target implant site in an idealized circular configuration

3.17 device embolization
dislodgement from the intended and documented original position to an unintended and non-therapeutic location

3.18 device failure
inability of a device to perform its intended function sufficient to cause a hazard

3.19 device migration
detectable movement or displacement of the device from its original position within the implant site, without embolization

3.20 effective orifice area
EOA
orifice area that has been derived from flow and pressure or velocity data

3.21 failure mode
mechanism of device failure

Note 1 to entry: Catastrophic support structure fracture, calcification and prolapse are examples of failure modes.

3.22 follow-up
continued assessment of patients who have received the heart valve substitute

3.23 forward flow volume
volume of flow ejected through the test heart valve substitute in the forward direction during one cycle
3.24  
fracture  
disruption, under the action of applied stress or strain, of any part of the transcatheter heart valve substitute that was previously intact

3.25  
heart valve substitute  
device used to replace the function of a natural valve of the heart

Note 1 to entry: See examples in Annex B.

3.26  
imaging modality  
imaging method used to facilitate delivery and/or retrieval of the implant within the target implant site, as well as to assess valve performance after implantation

3.27  
implant site  
intended site of transcatheter heart valve substitute deployment

3.28  
intended use  
use of a product, process or service in accordance with the specifications, instructions and information provided by the manufacturer

3.29  
leakage volume  
component of the regurgitant volume that is associated with leakage during closed phase of a valve in a single cycle and is the sum of the transvalvular leakage volume and paravalvular leakage volume

Note 1 to entry: The point of separation between the closing and leakage volumes is obtained according to a defined and stated criterion (the linear extrapolation shown in Figure 1 is just an example).

Note 2 to entry: See Figure 1.

3.30  
mean arterial pressure  
time-averaged arithmetic mean value of the arterial pressure during one cycle

3.31  
mean pressure difference  
time-averaged arithmetic mean value of the pressure difference across a heart valve substitute during the forward flow phase of the cycle

3.32  
non-structural valve dysfunction  
abnormality extrinsic to the transcatheter heart valve substitute that results in valve dysfunction (stenosis, regurgitation or both)

3.33  
occluder/leaflet  
component that inhibits back flow

Note 1 to entry: See examples in Annex B.

3.34  
paravalvular leakage volume  
component of the leakage volume that is associated with leakage around the closed heart valve substitute during a single cycle
3.35 reference valve
heart valve substitute with a known clinical experience used for comparative preclinical and clinical evaluations

3.36 regurgitant fraction
regurgitant volume expressed as a percentage of the forward flow volume

3.37 regurgitant volume
volume of fluid that flows through a heart valve substitute in the reverse direction during one cycle and is the sum of the closing volume and the leakage volume

Note 1 to entry: See Figure 1.

3.38 repositioning
change in implant position of a partially or fully deployed transcatheter heart valve substitute via a transcatheter technique, possibly requiring full or partial recapturing of the device

3.39 retrieval
removal of a partially or fully deployed transcatheter heart valve substitute via a transcatheter technique

3.40 risk
combination of the probability of occurrence of harm and the severity of that harm

Note 1 to entry: Adapted from ISO 14971.

3.41 risk analysis
systematic use of available information to identify hazards and to estimate the associated risks

Note 1 to entry: Adapted from ISO 14971.

3.42 risk assessment
overall process comprising a risk analysis and a risk evaluation

Note 1 to entry: Adapted from ISO 14971.

3.43 root mean square forward flow
RMS forward flow
square root of the integral of the volume flow rate waveform squared during the positive differential pressure interval of the forward flow phase used to calculate EOA

Note 1 to entry: See Figure 2.
Key title
1 aortic pressure
2 left ventricular pressure
3 aortic flow rate
a Positive pressure range.
b \( Q_{\text{rms}} \) range.

**Figure 2 — Schematic representation of the positive pressure period of an aortic forward flow interval**

3.44 safety
freedom from unacceptable risk

Note 1 to entry: Adapted from ISO 14971.

3.45 severity
measure of the possible consequences of a hazard

Note 1 to entry: Adapted from ISO 14971.

3.46 special processes
processes for which the product cannot be fully verified by inspection or test
3.47 **sterility assurance level**

SAL

probability of a single viable microorganism occurring on an item after sterilization

Note 1 to entry: The term SAL takes a quantitative value, generally $10^{-6}$ or $10^{-3}$. When applying this quantitative value to assurance of sterility, an SAL of $10^{-6}$ has a lower value but provides a greater assurance of sterility than an SAL of $10^{-3}$.

[ISO/TS 11139, definition 2.46]

3.48 **sterilization**

validated process used to render product free from viable microorganisms

Note 1 to entry: In a sterilization process, the nature of microbial inactivation is exponential and thus the survival of a microorganism on an individual item can be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero.

Note 2 to entry: See **sterility assurance level** (3.47).

Note 3 to entry: Adapted from ISO/TS 11139.

3.49 **structural component failure**

degradation of structural integrity of the support structure (e.g. strut fractures) that results in the functional performance of the implant no longer being acceptable and/or that results in adverse events

3.50 **structural valve dysfunction**

structural abnormality intrinsic to the transcatheter heart valve substitute that results in valve dysfunction (stenosis and/or transvalvular and/or paravalvular regurgitation)

3.51 **support structure**

portion of the transcatheter heart valve substitute that transfers loads between occluder and implant site and anchors the device within the implant site

3.52 **surgically implanted heart valve substitute**

heart valve substitute generally requiring direct visualization and cardiopulmonary bypass for implantation

3.53 **transcatheter heart valve substitute**

heart valve substitute implanted in a manner generally not involving direct visualization, and generally involving a beating heart

3.54 **transcatheter heart valve system**

implantable device, delivery system, accessories, packaging, labelling and instructions

3.55 **transvalvular leakage volume**

component of the leakage volume that is associated with leakage through the closed valve during a single cycle

3.56 **usability**

characteristic of the user interface that establishes effectiveness, efficiency, ease of user learning and user satisfaction
3.57 valve loading
process to affix or attach a transcatheter heart valve substitute onto a delivery device and collapse the valve (e.g. reduce its diameter) for insertion via the delivery system (e.g. catheter), performed either during manufacture or in the clinic

4 Abbreviations
For the purposes of this part of ISO 5840, the following abbreviations apply.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>EOA</td>
<td>Effective orifice area</td>
</tr>
<tr>
<td>AWT</td>
<td>Accelerated wear testing</td>
</tr>
<tr>
<td>CFD</td>
<td>Computational fluid dynamics</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>FEA</td>
<td>Finite element analysis</td>
</tr>
<tr>
<td>IFU</td>
<td>Instructions for use</td>
</tr>
<tr>
<td>LV</td>
<td>Left ventricle, left ventricular</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
</tbody>
</table>

5 Fundamental requirements
The manufacturer shall determine, at all stages of the product life cycle, the acceptability of the product for clinical use.

6 Device description
6.1 Intended use
The manufacturer shall identify the physiological condition(s) to be treated, the intended patient population, potential adverse events and intended claims.

6.2 Design inputs
6.2.1 Operational specifications
The manufacturer shall define the operational specifications for the device, including the principles of operation, intended device delivery approach/process, expected device lifetime, shelf life, shipping/storage limits, and the physiological environment in which it is intended to function. The manufacturer shall carefully define all relevant dimensional parameters that will be required to accurately select the size of device to be implanted. Table 1 and Table 2 define the expected physiological parameters of the intended adult patient population for transcatheter heart valve substitutes for both normal and pathological patient conditions.
### Table 1 — Heart valve substitute operational environment for left side of heart — Adult population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>General condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surrounding medium</td>
<td>Human heart/human blood</td>
</tr>
<tr>
<td>Temperature</td>
<td>34 °C to 42 °C</td>
</tr>
<tr>
<td>Heart rate</td>
<td>30 bpm to 200 bpm</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>3 l/min to 15 l/min</td>
</tr>
</tbody>
</table>

#### Blood pressures and resultant pressure loads by patient condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>Arterial peak systolic pressure mmHg</th>
<th>Arterial end diastolic pressure mmHg</th>
<th>Peak differential pressure across closed valve&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>120</td>
<td>80</td>
<td>100/mmHg, 120/mmHg</td>
</tr>
<tr>
<td>Hypotensive</td>
<td>60</td>
<td>40</td>
<td>50/mmHg, 60/mmHg</td>
</tr>
</tbody>
</table>

<sup>a</sup> Peak differential pressure across closed aortic valve is estimated using the following relationship:

\[
\Delta P_{Aortic} \approx \text{peak arterial systolic pressure} - \frac{1}{2} (\text{arterial end diastolic pressure} - \text{peak arterial systolic pressure})
\]

### Table 2 — Heart valve substitute operational environment for right side of heart — Adult population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>General condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surrounding medium</td>
<td>Human heart/human blood</td>
</tr>
<tr>
<td>Temperature</td>
<td>34 °C to 42 °C</td>
</tr>
<tr>
<td>Heart rate</td>
<td>30 bpm to 200 bpm</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>3 l/min to 15 l/min</td>
</tr>
<tr>
<td>Forward flow volume</td>
<td>25 ml to 100 ml</td>
</tr>
</tbody>
</table>

#### Blood pressures and resultant pressure loads by patient condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>Right ventricle peak systolic pressure mmHg</th>
<th>Pulmonary artery end diastolic pressure mmHg</th>
<th>Peak differential pressure across closed valve&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>18 to 35</td>
<td>8 to 15</td>
<td>13 to 25/mmHg, 18 to 35/mmHg</td>
</tr>
<tr>
<td>Hypotensive</td>
<td>15</td>
<td>5</td>
<td>10/mmHg, 15/mmHg</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>40 to 49</td>
<td>15 to 19</td>
<td>28 to 34/mmHg, 40 to 49/mmHg</td>
</tr>
<tr>
<td>Moderate</td>
<td>50 to 59</td>
<td>20 to 24</td>
<td>35 to 42/mmHg, 50 to 59/mmHg</td>
</tr>
</tbody>
</table>

<sup>a</sup> Peak differential pressure across closed pulmonary valve is estimated using the following relationship:

\[
\Delta P_{Pulmonary} \approx \text{peak pulmonary artery systolic pressure} - \frac{1}{2} (\text{pulmonary artery end diastolic pressure} - \text{peak pulmonary artery systolic pressure})
\]

Peak differential pressure across closed tricuspid valve estimated to be equivalent to right ventricle peak systolic pressure.
Table 2 (continued)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>General condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>60 to 84</td>
</tr>
<tr>
<td></td>
<td>25 to 34</td>
</tr>
<tr>
<td></td>
<td>43 to 59</td>
</tr>
<tr>
<td></td>
<td>60 to 84</td>
</tr>
<tr>
<td>Very severe</td>
<td>85 to 120</td>
</tr>
<tr>
<td></td>
<td>≥ 35</td>
</tr>
<tr>
<td></td>
<td>60 to 78</td>
</tr>
<tr>
<td></td>
<td>85 to 120</td>
</tr>
</tbody>
</table>

Peak differential pressure across closed pulmonary valve is estimated using the following relationship:

— $\Delta P_{\text{pulmonic}}$ approximate pressure associated with dicrotic notch assuming RV pressure is zero approximately pulmonary artery end diastolic pressure + $1/2$(right ventricle peak systolic pressure – pulmonary artery end diastolic pressure).

— Peak differential pressure across closed tricuspid valve estimated to be equivalent to right ventricle peak systolic pressure.

6.2.2 Performance specifications

The manufacturer shall establish (i.e. define, document and implement) the clinical performance requirements of the device and the corresponding device performance specifications for the intended use and device claims. The following list of desired clinical and device-based performance characteristics describe a safe and effective transcatheter heart valve substitute system.

6.2.2.1 Implantable device

The design attribute requirements of ISO 14630:2012, Clause 5, shall apply. The intended performance of the transcatheter heart valve substitute shall take into account at least the following:

a) the ability to be consistently, accurately and safely loaded onto the delivery system;

b) the ability to be consistently, accurately and safely deployed;

c) the ability to be safely retrieved and/or repositioned (if applicable);

d) the ability to ensure effective fixation within the target implant site;

e) the ability to maintain structural and functional integrity during the expected lifetime of the device;

f) the ability to conform with anatomical structures within the implant site (e.g. in the aortic position, there is potential for interaction with coronary ostia, anterior mitral leaflet, AV bundle branch);

g) the ability to allow forward flow with acceptably small mean pressure difference;

h) the ability to prevent retrograde flow with acceptably small regurgitation, including paravalvular leakage;

i) the ability to resist migration and embolization during the expected lifetime of the device;

j) the ability to minimize haemolysis;

k) the ability to minimize thrombus formation;

l) the ability to maintain its functionality for the intended application consistent with the target patient population.

6.2.2.2 Delivery system

The design attributes to meet the intended performance of the delivery system shall take into account at least the following:

a) the ability to permit consistent, accurate and safe access, delivery, placement and deployment of the transcatheter heart valve substitute to the intended implant site;

b) the ability to permit consistent and safe withdrawal of the delivery system prior to and after deployment of transcatheter heart valve substitute;
c) the ability to minimize haemolysis;
d) the ability to minimize thrombus formation;
e) the ability to minimize blood loss (haemostasis);
f) the ability to retrieve, reposition and/or remove the transcatheter heart valve substitute (if applicable).

6.2.2.3 Transcatheter heart valve system

The design attributes to meet the intended performance of the transcatheter heart valve system shall take into account at least the following:
a) the compliance of the transcatheter heart valve system with the requirements of ISO 10993-1 and appropriate other parts of ISO 10993;
b) the visibility of the transcatheter heart valve system under fluoroscopy or other imaging modalities;
c) compatibility with magnetic resonance imaging (MRI);
d) the ability of the transcatheter heart valve system to maintain its functionality and sterility for its specified shelf life prior to implantation.

6.2.3 Implant procedure

The entire system shall provide intended users with the ability to safely and effectively perform all required pre-operative, intra-operative and post-operative procedural tasks and achieve all desired objectives. This shall include all other tools and accessories that intended users will use to complete the procedure.

NOTE For guidance on how to determine and establish design attributes pertaining to the use of the system to conduct the implant procedure, see IEC 62366.

6.2.4 Packaging, labelling and sterilization

The transcatheter heart valve substitute system shall meet the requirements for packaging, labelling and sterilization contained within Annex C, Annex D and Annex E, respectively.

The manufacturer shall provide sufficient information and guidance in the labelling to allow for appropriate preparation of the implant site (e.g. balloon valvuloplasty), accurate selection of appropriate implant size and reliable implantation of the transcatheter heart valve substitute.

6.3 Design outputs

The manufacturer shall establish (i.e. define, document and implement) a complete specification of the transcatheter heart valve substitute system, including component and assembly-level specifications, delivery system, accessories, packaging and labelling. Annex F contains a listing of terms that may be used in describing various valve models. In addition to the physical components of the heart valve substitute system, the implant procedure itself should be considered an important element of safe and effective heart valve therapy.

6.4 Design transfer (manufacturing verification/validation)

The manufacturer shall generate a flowchart identifying the manufacturing process operations and inspection steps. The flowchart shall indicate the input of all components and important manufacturing materials.

As part of the risk management process, the manufacturer shall establish the control measures and process conditions necessary to ensure that the device is safe and suitable for its intended use. The risk management file shall identify and justify the verification activities necessary to demonstrate the acceptability of the process ranges chosen.