American National Standard

ANSI/AAMI/ISO 12417-1:2015

Cardiovascular implants and extracorporeal systems—Vascular device-drug combination products—Part 1: General requirements

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Objectives and uses of AAMI standards and recommended practices

It is most important that the objectives and potential uses of an AAMI product standard or recommended practice are clearly understood. The objectives of AAMI's technical development program derive from AAMI's overall mission: the advancement of medical instrumentation. Essential to such advancement are (1) a continued increase in the safe and effective application of current technologies to patient care, and (2) the encouragement of new technologies. It is AAMI's view that standards and recommended practices can contribute significantly to the advancement of medical instrumentation, provided that they are drafted with attention to these objectives and provided that arbitrary and restrictive uses are avoided.

A voluntary *standard* for a *medical device* recommends to the manufacturer the information that should be provided with or on the product, basic safety and performance criteria that should be considered in qualifying the device for clinical use, and the measurement techniques that can be used to determine whether the device conforms with the safety and performance criteria and/or to compare the performance characteristics of different products. Some standards emphasize the information that should be provided with the device, including performance characteristics, instructions for use, warnings and precautions, and other data considered important in ensuring the safe and effective use of the device in the clinical environment. Recommending the disclosure of performance characteristics often necessitates the development of specialized test methods to facilitate uniformity in reporting; reaching consensus on these tests can represent a considerable part of committee work. When a drafting committee determines that clinical concerns warrant the establishment of *minimum* safety and performance criteria, referee tests must be provided and the reasons for establishing the criteria must be documented in the rationale.

A *recommended practice* provides guidelines for the use, care, and/or processing of a medical device or system. A recommended practice does not address device performance *per se*, but rather procedures and practices that will help ensure that a device is used safely and effectively and that its performance will be maintained.

Although a device standard is primarily directed to the manufacturer, it may also be of value to the potential purchaser or user of the device as a frame of reference for device evaluation. Similarly, even though a recommended practice is usually oriented towards healthcare professionals, it may be useful to the manufacturer in better understanding the environment in which a medical device will be used. Also, some recommended practices, while not addressing device performance criteria, provide guidelines to industrial personnel on such subjects as sterilization processing, methods of collecting data to establish safety and efficacy, human engineering, and other processing or evaluation techniques; such guidelines may be useful to health care professionals in understanding industrial practices.

In determining whether an AAMI standard or recommended practice is relevant to the specific needs of a potential user of the document, several important concepts must be recognized:

All AAMI standards and recommended practices are *voluntary* (unless, of course, they are adopted by government regulatory or procurement authorities). The application of a standard or recommended practice is solely within the discretion and professional judgment of the user of the document.

Each AAMI standard or recommended practice reflects the collective expertise of a committee of health care professionals and industrial representatives, whose work has been reviewed nationally (and sometimes internationally). As such, the consensus recommendations embodied in a standard or recommended practice are intended to respond to clinical needs and, ultimately, to help ensure patient safety. A standard or recommended practice is limited, however, in the sense that it responds generally to perceived risks and conditions that may not always be relevant to specific situations. A standard or recommended practice is an important *reference* in responsible decision-making, but it should never *replace* responsible decision-making.

Despite periodic review and revision (at least once every five years), a standard or recommended practice is necessarily a static document applied to a dynamic technology. Therefore, a standards user must carefully review the reasons why the document was initially developed and the specific rationale for each of its provisions. This review will reveal whether the document remains relevant to the specific needs of the user.

Particular care should be taken in applying a product standard to existing devices and equipment, and in applying a recommended practice to current procedures and practices. While observed or potential risks with existing equipment typically form the basis for the safety and performance criteria defined in a standard, professional judgment must be used in applying these criteria to existing equipment. No single source of information will serve to identify a particular product as "unsafe". A voluntary standard can be used as one resource, but the ultimate decision as to product safety and efficacy must take into account the specifics of its utilization and, of course, cost-benefit considerations. Similarly, a recommended practice should be analyzed in the context of the specific needs and resources of the individual institution or firm. Again, the rationale accompanying each AAMI standard and recommended practice is an excellent guide to the reasoning and data underlying its provision.

In summary, a standard or recommended practice is truly useful only when it is used in conjunction with other sources of information and policy guidance and in the context of professional experience and judgment.

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Requests for interpretations of AAMI standards and recommended practices must be made in writing, to the AAMI Vice President, Standards Policy and Programs. An official interpretation must be approved by letter ballot of the originating committee and subsequently reviewed and approved by the AAMI Standards Board. The interpretation will become official and representation of the Association only upon exhaustion of any appeals and upon publication of notice of interpretation in the "Standards Monitor" section of the *AAMI News*. The Association for the Advancement of Medical Instrumentation disclaims responsibility for any characterization or explanation of a standard or recommended practice which has not been developed and communicated in accordance with this procedure and which is not published, by appropriate notice, as an *official interpretation* in the *AAMI News*.

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Cardiovascular implants and extracorporeal systems—Vascular device-drug combination products—Part 1: General requirements

Developed by
Association for the Advancement of Medical Instrumentation

Approved 16 November 2015 by
American National Standards Institute, Inc.

Abstract: Specifies requirements for vascular device-drug combination products based upon current technical and medical knowledge. Outlines requirements for intended performance, design attributes, materials, design evaluation, manufacturing, sterilization, packaging, and information supplied by the manufacturer.

Keywords: analysis, biocompatibility, clinical, design, evaluation, matrix, performance, pharmaceutical, VDDCP

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Glossary of equivalent standards

International Standards adopted in the United States may include normative references to other International Standards. AAMI maintains a current list of each International Standard that has been adopted by AAMI (and ANSI). Available on the AAMI website at the address below, this list gives the corresponding U.S. designation and level of equivalency to the International Standard.

www.aami.org/standards/glossary.pdf

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Committee representation

Association for the Advancement of Medical Instrumentation

Vascular Device-Drug Combination Products Working Group

The adoption of ISO 12417-1:2015 as an American National Standard was initiated by the AAMI Vascular Device-Drug Combination Products Working Group. The AAMI Vascular Device-Drug Combination Products Working Group also functions as a U.S. Technical Advisory Group to the relevant work in the International Organization for Sterilization (ISO). U.S. representatives from the AAMI Vascular Device-Drug Combination Products Working Group (U.S. Sub-TAG for ISO/TC 150/SC 2/WG 6, Vascular device-drug combination products) played an active part in developing the ISO standard.

At the time this document was published, the **AAMI Vascular Device-Drug Combination Products Working Group** had the following members:

Chairs:
Stephanie Del Paine, PhD, Cook Research
Jennifer Goode, FDA/CDRH/ ODE/DCD

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Richard Chan, CCP, Northshore University Hospital - Long Island University
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NOTE—Participation by federal agency representatives in the development of this standard does not constitute endorsement by the federal government or any of its agencies.

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Background on AAMI adoption of ISO 12417-1:2015

As indicated in the foreword to the main body of this document (page viii), the International Organization for Standardization (ISO) is a worldwide federation of national standards bodies. The United States is one of the ISO members that took an active role in the development of this standard, which was developed by ISO Technical Committee 150, Subcommittee 2, *Cardiovascular implants and extracorporeal systems*, to fill a need for general requirements for vascular device-drug combination products. This standard revises and replaces ISO Technical Specification (TS) 12417:2011, *Cardiovascular implants and extracorporeal systems – Vascular device-drug combination products*.

U.S. participation in this ISO TC is organized through the U.S. Technical Advisory Group for ISO/TC 150/SC 2, administered by the Association for the Advancement of Medical Instrumentation (AAMI). The U.S. TAG for ISO/TC 150/SC 2 supports the guidance provided in this document.

The AAMI adoption of AAMI/ISO 12417-1:2015 was approved by AAMI on 16 November 2016 to revise and replace ANSIA/AAMI/ISO Technical Information Report (TIR) 12417:2011, *Cardiovascular implants and extracorporeal systems – Vascular device-drug combination products*. The AAMI Vascular Device-Drug Combination Products Working Group (U.S. sub-TAG for ISO/TC 150/SC 2/WG 6, Vascular device-drug combination products) initiated the U.S. adoption of ISO 12417-1:2015.

AAMI and ANSI procedures require that standards be reviewed and, if necessary, revised every five years to reflect technological advances that may have occurred since publication.

AAMI (and ANSI) have adopted other ISO standards. See the Glossary of Equivalent Standards for a list of ISO standards adopted by AAMI which gives the corresponding U.S. designation and the level of equivalency with the ISO standard.

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data come to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 4301 N. Fairfax Drive, Suite 301, Arlington, VA 22203-1633.

NOTE—Beginning with the foreword on page viii, this ANSI/AAMI/ISO standard is identical to ISO 12417-1:2015.

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Foreword

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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

ISO 12417 consists of the following parts under the general title, *Cardiovascular implants and extracorporeal systems — Vascular device-drug combination products*:

— *Part 1: General requirements*

— *Part 2: Local regulatory guidance*

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Introduction

This part of ISO 12417 was prepared in order to provide minimum requirements for vascular device-drug combination products (VDDCPs).

Only issues related to vascular devices combined with drug(s), wherein the drug serves an ancillary function of the VDDCP are covered by this part of ISO 12417.

It was impossible, when writing this part of ISO 12417, to take into consideration all future and emerging technologies. VDDCPs using such technologies will need to be evaluated following the basic requirements of this International Standard. Testing beyond the scope of this part of ISO 12417 might also be necessary to characterize these device systems. Consideration shall be given to the failure modes of the VDDCP and their effects on the performance in deciding what testing will be appropriate.

For issues related to the primary mode of action (PMOA) of the vascular VDDCP, the reader might find it useful to consider a number of other International Standards (see Bibliography).

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Cardiovascular implants and extracorporeal systems—Vascular device-drug combination products—Part 1: General requirements

1 Scope

This part of ISO 12417 specifies requirements for vascular device-drug combination products (VDDCPs) based upon current technical and medical knowledge. VDDCPs are medical devices with various clinical indications for use in the human vascular blood system. A VDDCP incorporates, as an integral part, substance(s) which, if used separately, can be considered to be a medicinal substance or product (drug substance, drug product) but the action of the medicinal substance is ancillary to that of the device and supports the primary mode of action (PMOA) of the device. With regard to safety, this part of ISO 12417 outlines requirements for intended performance, design attributes, materials, design evaluation, manufacturing, sterilization, packaging, and information supplied by the manufacturer. For implanted products, this International Standard should be considered as a supplement to ISO 14630, which specifies general requirements for the performance of non-active surgical implants. This International Standard should also be considered as a supplement to relevant device-specific standards, such as the ISO 25539-series specifying requirements for endovascular devices. Requirements listed in this part of ISO 12417 also address VDDCPs that are not permanent implants.

NOTE Due to variations in the design of combination products covered by this part of ISO 12417 and due to the relatively recent development of some of these combination products, acceptable standardized *in vitro* test results and clinical study results are not always available. As further scientific and clinical data become available, appropriate revision of this part of ISO 12417 might be necessary.

Delivery systems or parts of the delivery system are included in the scope of this part of ISO 12417, if they comprise an integral component of the vascular device and if they are drug-covered (e.g. drug-covered balloon catheters and drug-covered guidewires).

Devices whose PMOA is to provide a conduit for delivery of a drug, are excluded from the scope of this part of ISO 12417 (e.g. infusion catheters), unless they contain a drug component that is intended to have an ancillary action to the device part (e.g. antimicrobial coated infusion catheter).

Procedures and devices used prior to and following the introduction of the VDDCP (e.g. balloon angioplasty devices) are excluded from the scope of this part of ISO 12417 if they do not affect the drug-related aspects of the device.

This part of ISO 12417 is not comprehensive with respect to the pharmacological evaluation of VDDCPs. Some information on the requirements of different national and regional authorities is given in Annex B.

Absorbable components of VDDCPs (e.g. coatings) are addressed by this part of ISO 12417 in their connection with drug-related aspects of the device. Degradation and other time-dependent aspects of absorbable implants and coatings are not completely addressed by this part of ISO 12417.

NOTE See also ISO/TS 17137 and ASTM F3036-13.

This part of ISO 12417 does not address issues associated with viable or non-viable biological materials such as tissues, cells, or proteins.

This part of ISO 12417 does not address issues associated with active surgical implants (i.e. implants that require power not generated by the human body or gravity).

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2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. 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 — Animal welfare requirements*

ISO 10993-7, *Biological evaluation of medical devices — Ethylene oxide sterilization residuals*

ISO 11070, *Sterile single-use intravascular introducers, dilators and guidewires*

ISO 11607-1, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

ISO 14155, *Clinical investigation of medical devices for human subjects — Good clinical practice*

ISO 14630:2012, *Non-active surgical implants — General requirements*

ISO 14937, *Sterilization of health care products — General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices*

ISO 14971:2007, *Medical devices — Application of risk management to medical devices*

ISO 15223-1, *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied — Part 1: General requirements*

ISO 25539-2, *Cardiovascular implants — Endovascular devices — Part 2: Vascular stents*

NOTE See the Bibliography for additional device-specific and regional information about standards and guidance documents.

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 14630 and the following apply.

NOTE Potential clinical events are defined in Annex A.

3.1
active pharmaceutical ingredient
API
drug
pharmacologically active (drug or medicinal) substance used as a raw material, which is coated on, bound to or incorporated into the device to achieve an ancillary device function (e.g. minimizing vascular restenosis)

3.2
batch
quantity of VDDCP at the final stage or pre-final stage of manufacture which has undergone the same manufacturing cycle, using the same components (e.g. same coating solution, same device size), and meets the same specifications

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3.3
change
alteration to an activity or to the VDDCP to improve or maintain the composition or performance of a VDDCP

3.4
clinical event
complication, failure, or device-related observation that might be observed with clinical use of a VDDCP

Note 1 to entry: Such events might not have clinical significance and might not be attributable to the VDDCP.

3.5
compendial pharmaceutical reference standard
general term covering reference substances, reference preparations, and reference spectra that are recognized by a national pharmacopoeia

3.6
device part of the VDDCP
DP
part of the VDDCP intended to treat vascular disease by temporary or long-term intervention or implantation that does not achieve its PMOA in or on the human body by pharmacological, immunological, or metabolic means, but might be assisted in its function by such means

3.7
drug assay
biological or chemical method to determine the activity or potency of a substance

3.8
drug product
medicinal product
API, in its final form for administration to the patient (e.g. tablet, solution, spray), that is intended to prevent, diagnose, or treat disease and that achieves its principal intended action in or on the body by pharmacological, immunological, or metabolic means

3.9
drug-containing part of the VDDCP
DCP
part of the VDDCP that consists of the API or matrix and associated device interfaces intended to assist in the PMOA of the device and/or diminish or ameliorate an unintended effect that placement of the device part might stimulate

Note 1 to entry: Some VDDCPs might have an incorporated medicinal or drug substance primarily intended to optimize the surface properties of the VDDCP.

3.10
DCP interface
common boundary or interconnection between the various components of the device part(s) and the drug-containing part(s) of a VDDCP

EXAMPLES

a) the interface between the matrix containing the API and packaging materials with direct DCP contact;

b) the device surface(s);

c) the interface between the matrix and the API.

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3.11
delivery system
transport device that physically or mechanically positions the VDDCP and/or the DCP at the intended anatomic location

EXAMPLE: The delivery system of a drug-coated balloon, would position the balloon in the lumen of the lesion intended to be treated.

3.12
drug content
total labelled amount of API in a VDDCP

Note 1 to entry: Drug content might be expressed as µg/DCP of a certain size.

3.13
drug delivery
local interaction between the VDDCP drug and the *in vivo* environment, whether the drug is released from, eluted from, or remains bound to the VDDCP

3.14
drug-related impurity
any substance in the DCP of a VDDCP that is not the API or an excipient

Note 1 to entry: Drug-related impurities might include drug degradation products or degradants, drug-synthesis-related impurities, isomers of the drug, residual drug solvents, or biologic contaminants (e.g. occurring with drugs derived from biologic systems).

3.15
drug release characterization
in vitro characterization of the API released from the DCP of a VDDCP over time

EXAMPLE: The release might be determined by a drug elution test, and could include a curve shape (or profile), a drug release rate, or both.

3.16
durability
ability to maintain adequate integrity and robustness during procedural (i.e. access, deployment, withdrawal), post-procedural, and long-term use (i.e. over time) in accordance with the design specifications

3.17
efficacy
effectiveness
ability of the VDDCP to achieve the planned and desired physiological result

3.18
evaluate
appraise or analyze qualitatively

3.19
excipient
additional material(s), other than the API, that are intentional components of the drug-containing part of a VDDCP

EXAMPLES: Filler, extender, diluent, wetting agent, solvent, colorant, stabilizer, antioxidant, preservative, pH maintainer, polymers, adhesives.

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3.20
functionality
ability of the VDDCP to perform physically, chemically, and/or mechanically, as designed

Note 1 to entry: Functionality does not include the physiological response to the VDDCP (i.e. efficacy).

3.21
matrix
any organic or inorganic material, other than living cells, intentionally applied by a manufacturer to a vascular device and designed for the purpose of drug storage, local drug activity at the surface and/or enabling, retarding, delaying, or modifying drug release

Note 1 to entry: The matrix might: be permanent or temporary (dissolvable, absorbable or degradable); include surface treatments such as primers; be a coating with or without an API, or consist of multiple excipients and/or multiple APIs.

3.22
particulates
particles
mobile matter, other than gas bubbles, present on, or arising from the use of the VDDCP

3.23
pharmacokinetics
absorption, distribution, metabolism, and elimination of a drug *in vivo*

3.24
procedural fluids
blood and serum, saline, and contrast media that come into contact with a VDDCP

3.25
stability studies
tests undertaken according to a prescribed stability protocol to establish, support, or confirm the shelf life of a VDDCP

Note 1 to entry: Additional guidance on the drug-related aspects of the drug-containing part of the VDDCP can be found in International Conference on Harmonization Guideline ICH Q1A.

3.26
uniformity of drug content
comparison of the uniformity of the drug content between individual VDDCPs within each batch as compared to the labelled claim

3.27
vascular device-drug combination product
VDDCP
vascular medical device (PMOA) that incorporates one or more APIs as an integral part (ancillary mode of action)

3.28
VDDCP deployment
physical or mechanical positioning of the VDDCP so that the drug-containing part is in contact with the intended anatomic treatment site

Note 1 to entry: The VDDCP might be permanently deployed (e.g. a drug-eluting stent) or temporarily deployed (e.g. a drug-eluting balloon).

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3.29
VDDCP specification
required list of test procedures and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described

Note 1 to entry: A specification is a critical quality standard. It establishes the set of criteria to which a VDDCP has to conform.

Note 2 to entry: Additional guidance on the drug-related aspects of the drug-containing part of the VDDCP can be found in International Conference on Harmonization Guideline ICH Q6A.

4 Intended performance

4.1 General

The requirements of ISO 14630:2012, Clause 4, shall apply.

4.2 Classification

A VDDCP is a product that is considered to be a medical device but which incorporates, as an integral part, substances which, if used separately, can be considered to be a medicinal product or drug product. It is classified as a medical device, provided that the action of the medicinal or drug substance is ancillary to that of the device, as reflected in the product claim and as supported by the scientific data provided by the manufacturer of the device.

4.3 Intended clinical location

The intended clinical location shall be identified as one or more of the following:

a) abdominal aorta;

b) arterio-venous shunt for vascular access;

c) carotid;

d) coronary;

e) femoral;

f) iliac;

g) popliteal;

h) intracerebral;

i) renal;

j) thoracic aorta;

k) thoraco-abdominal aorta;

l) tibial;

m) other arterial or venous vessels to be specified.

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5 Design attributes

5.1 General

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

a) ability of the device part of the VDDCP (i.e. the device without the API and matrix) to fulfill all product-specific requirements for the PMOA (e.g. the mechanical function), which are defined in the device-related standards;

b) ability of the drug-containing part of the VDDCP to fulfill the drug-specific function and requirements of the VDDCP as defined in 5.2.

5.2 Drug-containing part of the VDDCP (DCP)

5.2.1 General

The design attributes of the VDDCP to meet the intended performance of the DCP shall additionally take into account at least the following:

a) ability of the DCP to be consistently, accurately, and safely brought into contact with the intended anatomic treatment site;

b) appropriate physical and chemical compatibility of the DCP interfaces (i.e. the device, the drug, the matrix, and any packaging with direct DCP contact);

c) appropriate biocompatibility of the DCP;

d) conformance of the DCP to VDDCP specifications at the time of manufacture and after storage;

e) ability of the DCP to deliver or maintain the intended amount of drug safely at the target site in accordance with the specification of the VDDCP at product release and for the duration of the labelled shelf life;

f) appropriate interaction between the VDDCP and procedural fluids.

5.2.2 Matrix

The design attributes of the VDDCP to meet the intended performance of the matrix shall additionally take into account at least the following:

a) ability of the matrix to maintain adequate integrity during procedural use and over time in accordance with the design specifications (e.g. freedom from significant delamination, flaps, and bare spots);

b) ability of the matrix to maintain adequate resistance to unintended generation of particles;

c) conformance of the matrix to VDDCP specifications at the time of manufacture and after storage;

d) conformance of the matrix dimensions, physical and chemical properties, and other matrix parameters (e.g. porosity, mass, density, distribution, glass transition temperature, melting temperature, fragmentation point) to the design requirements;

e) if soluble or degradable, the ability of the matrix to control the release of drug and the interaction of any solubilized or degradation products with the body (i.e. biocompatibility of the matrix as well as the degradation products);

f) effect of imaging (e.g. the heating caused by magnetic resonance imaging [MRI]) on the matrix.

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