INSIGNEO

Institute for *in silico* Medicine

The emerging regulatory framework for *in silico* medicine

Marco Viceconti, Shreya Barlingay, Rachel Morecroft, and Andrii Grytsan

The University Of Sheffield.

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

The University of Sheffield

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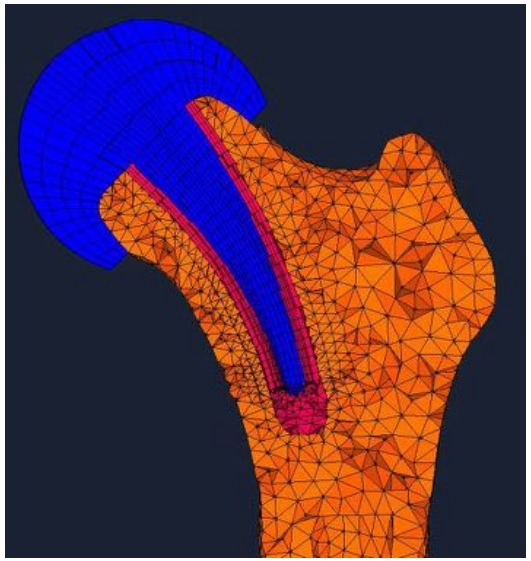
Marco Viceconti - About me

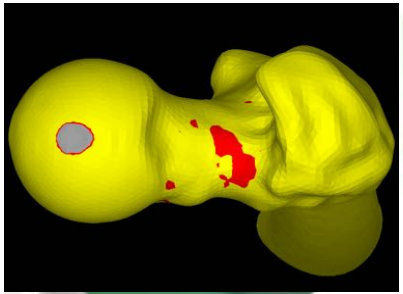
1989 - Orthopaedic devices

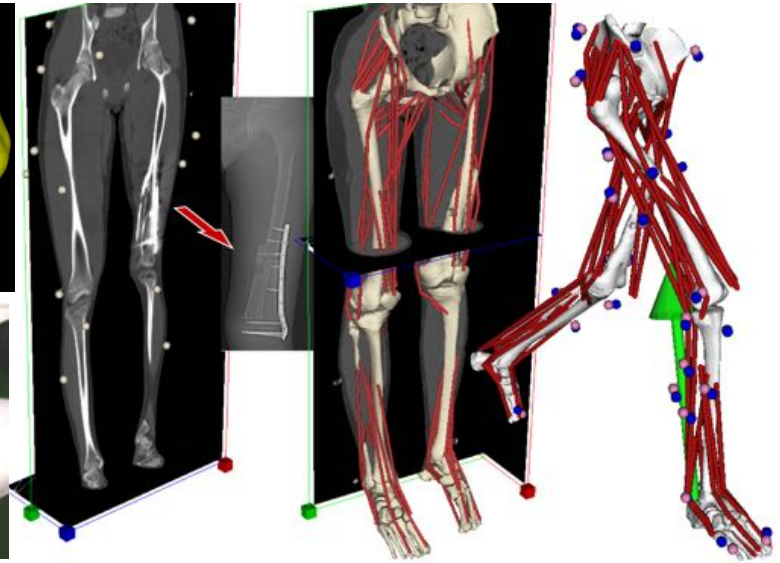
1996 - Computational biomechanics

2002 - Subject-specific modelling

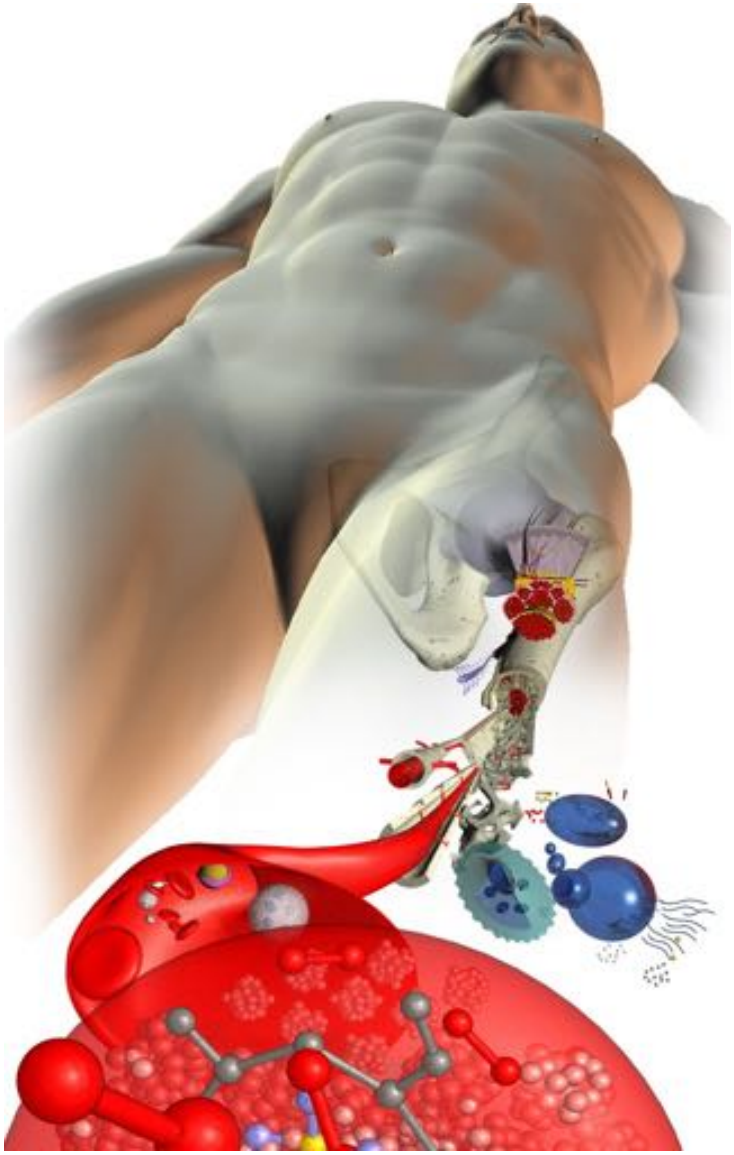
2007 - In silico Medicine







Terminology



- **In silico Medicine**: the use of subject-specific computer modelling & simulation in healthcare; technologies for **predictive medicine**
  - **Digital Patient**: Decision Support System for diagnosis, prognosis or treatment planning
  - **In Silico Clinical Trial**: development or regulatory evaluation of a medicinal product or medical device/medical intervention
  - **Personal Health Forecasting**: advice citizen/patient on how to best self-manage health risks or chronic conditions
- **Virtual Physiological Human**: Framework of methods and technologies that enables the investigation of the human body as a single complex system

In Silico Medicine

VPH Institute - 2010

VPH Institute
Building the Virtual Physiological Human

STEP – 2007

Insigneo - 2012

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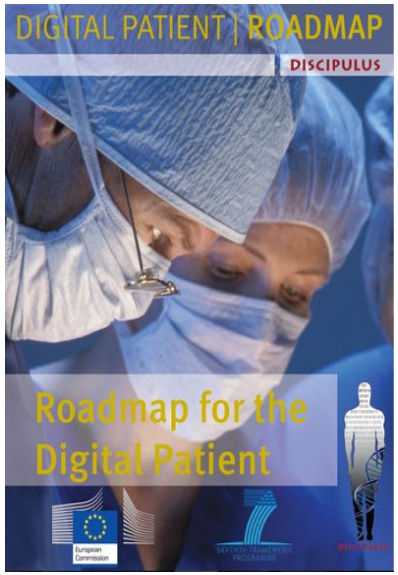
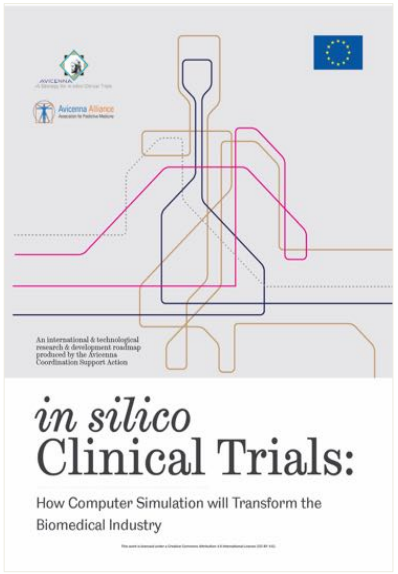
DISCIPULUS– 2011



AVICENNA– 2013



Insigneo Graduate Studies

MEC42 - Regulatory Affairs for Medical Devices

BIE6432 – Emerging regulatory pathways for *in silico* medicine

The beginnings

1964: IBM System/360

By Wolfgang Manousek from Dormagen, Germany (Flickr) [CC BY 2.0], via Wikimedia Commons

1970 – DEC PDP-11

- Mini-computers, and later personal computers make their first appearances
- Transactional systems are installed in specific department such as pharmacy to track recurrent events

By Stefan_Kögl (Own work) [CC-BY-SA-3.0], via Wikimedia Commons

1982: Therac-25

In 1982 AECL produced the Therac-25 radiation therapy machine controlled by a PDP-11 computer

Between 1985 and 1987 six patients received by accident massive radiations doses and three died of radiation poisoning

The problem was found to be a “bug” in the control software

N. G. Leveson and C. S. Turner, "An investigation of the Therac-25 accidents," in *Computer*, vol. 26, no. 7, pp. 18-41, July 1993.

Quality assurance for software

Software quality assurance

1991 ➔ ISO/IEC 9126 “Software engineering -- Product quality”

1997 ➔ ISO 9000-3 “Quality management and quality assurance standards -- Part 3: Guidelines for the application of ISO 9001:1994 to the development, supply, installation and maintenance of computer software”

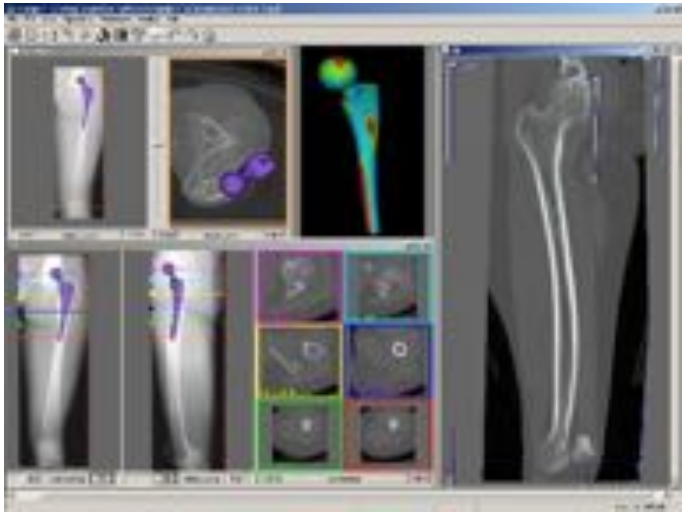
Image curtesy of http://agilesoftwaresolutions.com

2000's: Software gets inside

Software enter inside medical devices: pacemakers and ICDs become programmable

implantable cardioverter-defibrillator

By n28ive1 on Flickr [CC BY 2.0], via Wikimedia Commons



HipOp CT-based THR planning SW, 2000

The growth of computer-assisted surgery drives the importance of surgical planning software

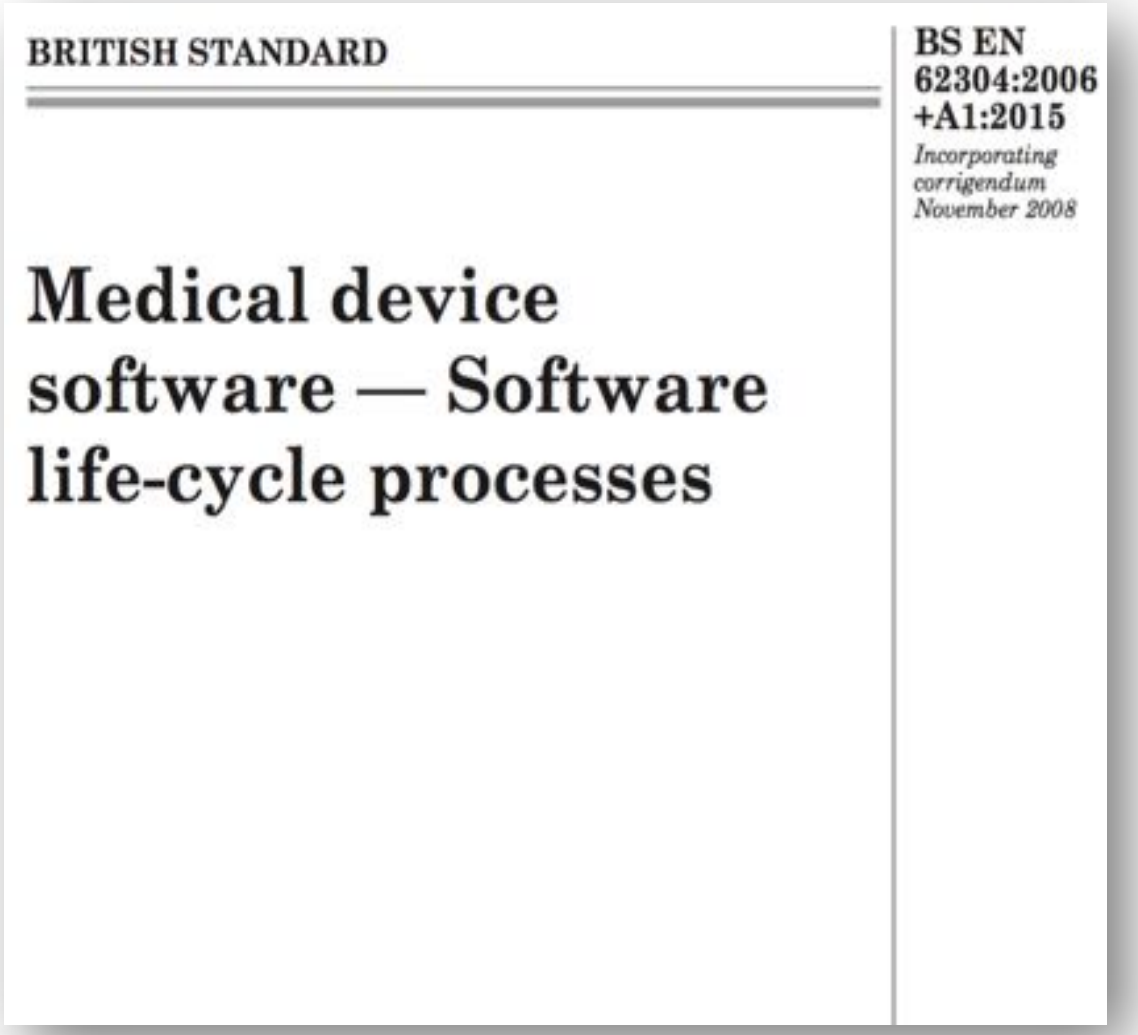
Software as a medical device

2007/47/EC: ammend definition

"*medical device* means any instrument, apparatus, appliance, **software**, material or other article […] including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes …"

"Stand alone software is considered to be an **active** medical device".

EN 62304:2006

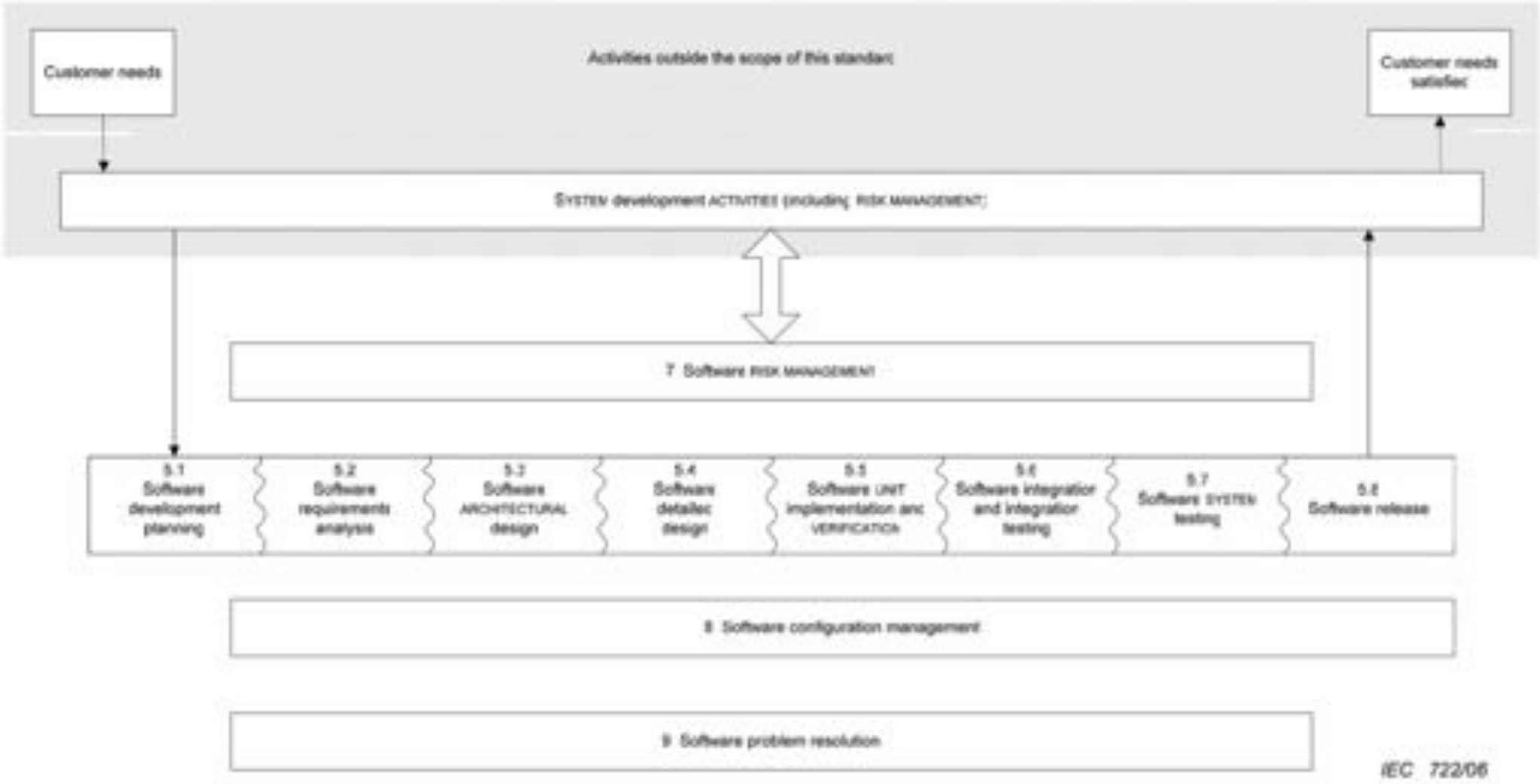

BRITISH STANDARD

BS EN 62304:2006 +A1:2015

Incorporating corrigendum November 2008

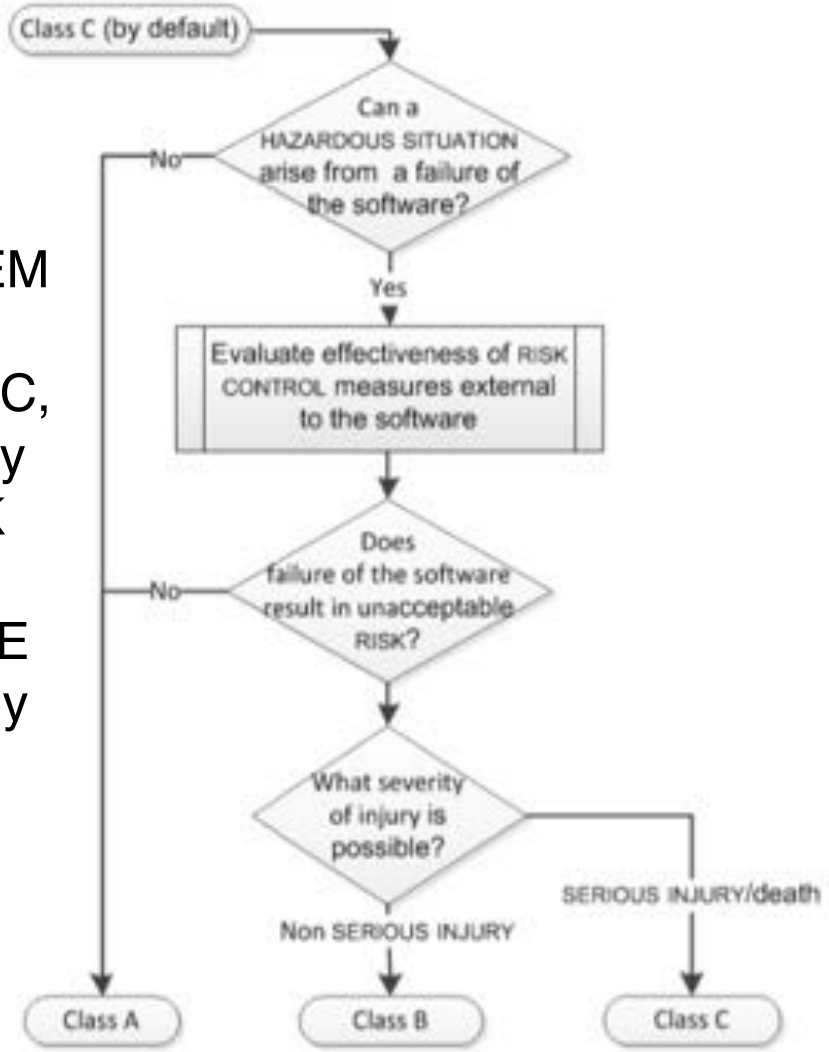
Medical device software — Software life-cycle processes

SW development process



Software safety classes

For a SOFTWARE SYSTEM initially classified as software safety class B or C, the MANUFACTURER may implement additional RISK CONTROL measures external to the SOFTWARE SYSTEM and subsequently assign a new software safety classification to the SOFTWARE SYSTEM.



In determining the software safety classification of the SOFTWARE SYSTEM:

- *Probability of a software failure shall be assumed to be 1.*
- *Only RISK CONTROL measures not implemented within (external to) the SOFTWARE SYSTEM shall be considered.*

NOTE: Such RISK CONTROL measures may reduce the probability that a software failure will cause HARM, and/or the severity of that HARM.

Note: A SOFTWARE SYSTEM which implements RISK CONTROL measure may fail, and this may contribute to a HAZARDOUS SITUATION. The resulting HARM may include the HARM which the RISK CONTROL measure is designed to prevent (see 7.2.2b)

IEC

ISO9000-3 vs EN62304

- While ISO 9000-3 focused on **quality** management system for software development, EN62304 stresses the crucial importance of **risk** management system and risk control, acknowledging that:
  - 'There is no known method to guarantee 100% SAFETY for any kind of software' (Annex B.4)
  - 'testing of software is not sufficient to determine that it is safe in operation' (Annex A.1).

SaMD: clinical evaluation

IMDRF International Medical Device Regulators Forum

PROPOSED DOCUMENT

International Medical Device Regulators Forum

Title: Software as a Medical Device (SaMD): Clinical Evaluation

Authoring Group: Software as a Medical Device Working Group

Date: 5 August 2016

SW supports clinical decision

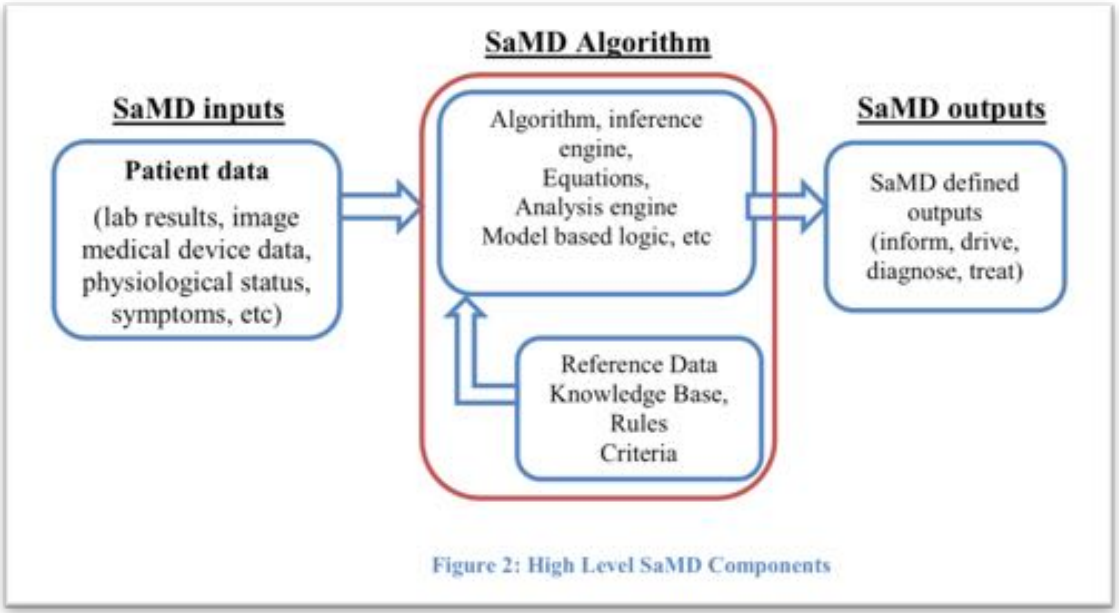


Figure 2: High Level SaMD Components

EUROPEAN COMMISSION
DG Internal Market, Industry, Entrepreneurship and SMEs
Directorate Consumer, Environmental and Health Technologies
Unit Health technology and Cosmetics

MEDICAL DEVICES: Guidance document

Qualification and Classification of stand alone software

MEDDEV 2.1/6
July 2016

GUIDELINES ON THE QUALIFICATION AND CLASSIFICATION OF STAND ALONE SOFTWARE USED IN HEALTHCARE WITHIN THE REGULATORY FRAMEWORK OF MEDICAL DEVICES

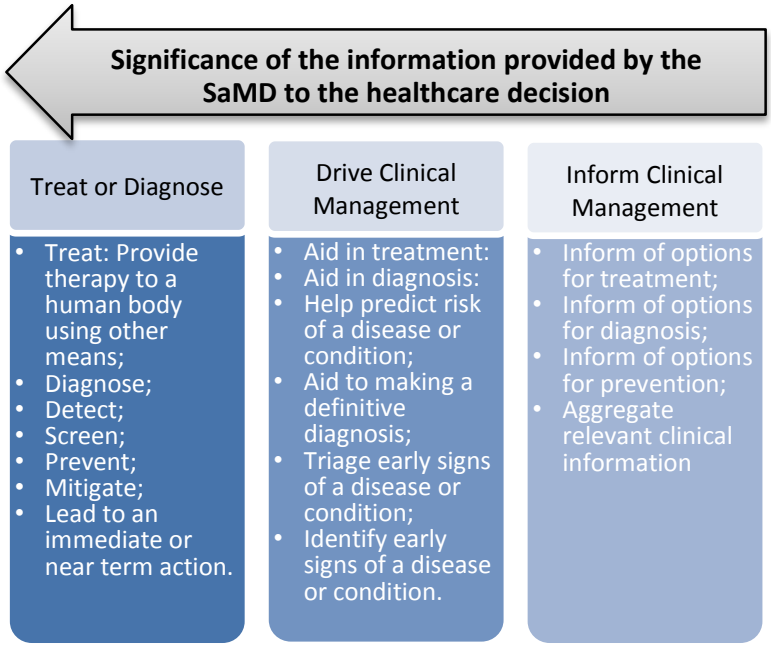


Figure 3 – *SaMD N12* components of "significance" of SaMD output (See Section 8.1 of this document)

Before and after SaMD

BEFORE

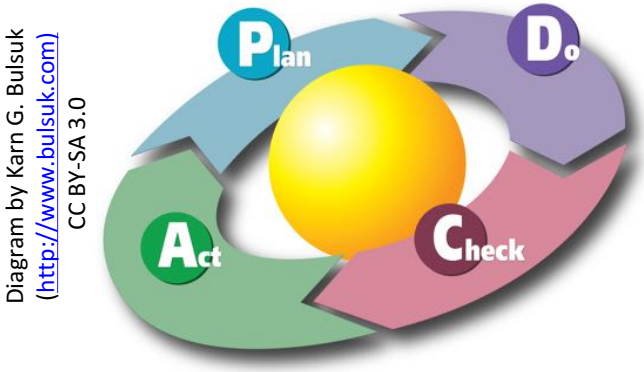


Diagram by Karn G. Bulsuk (http://www.bulsuk.com) CC BY-SA 3.0

AFTER

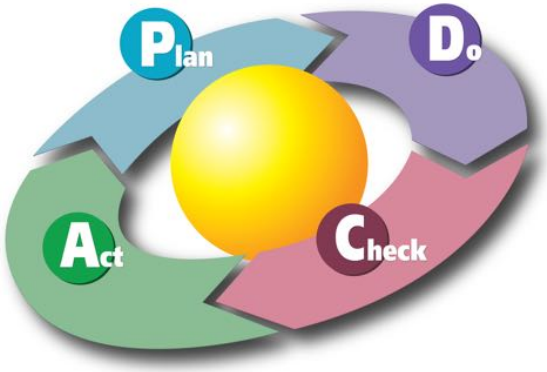
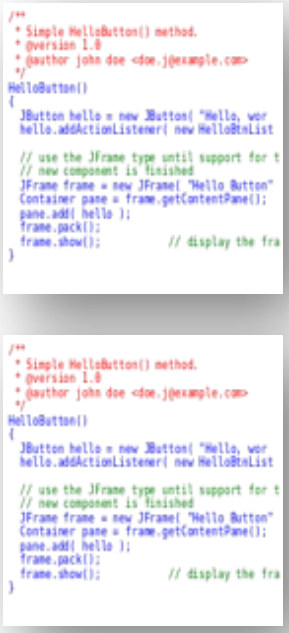


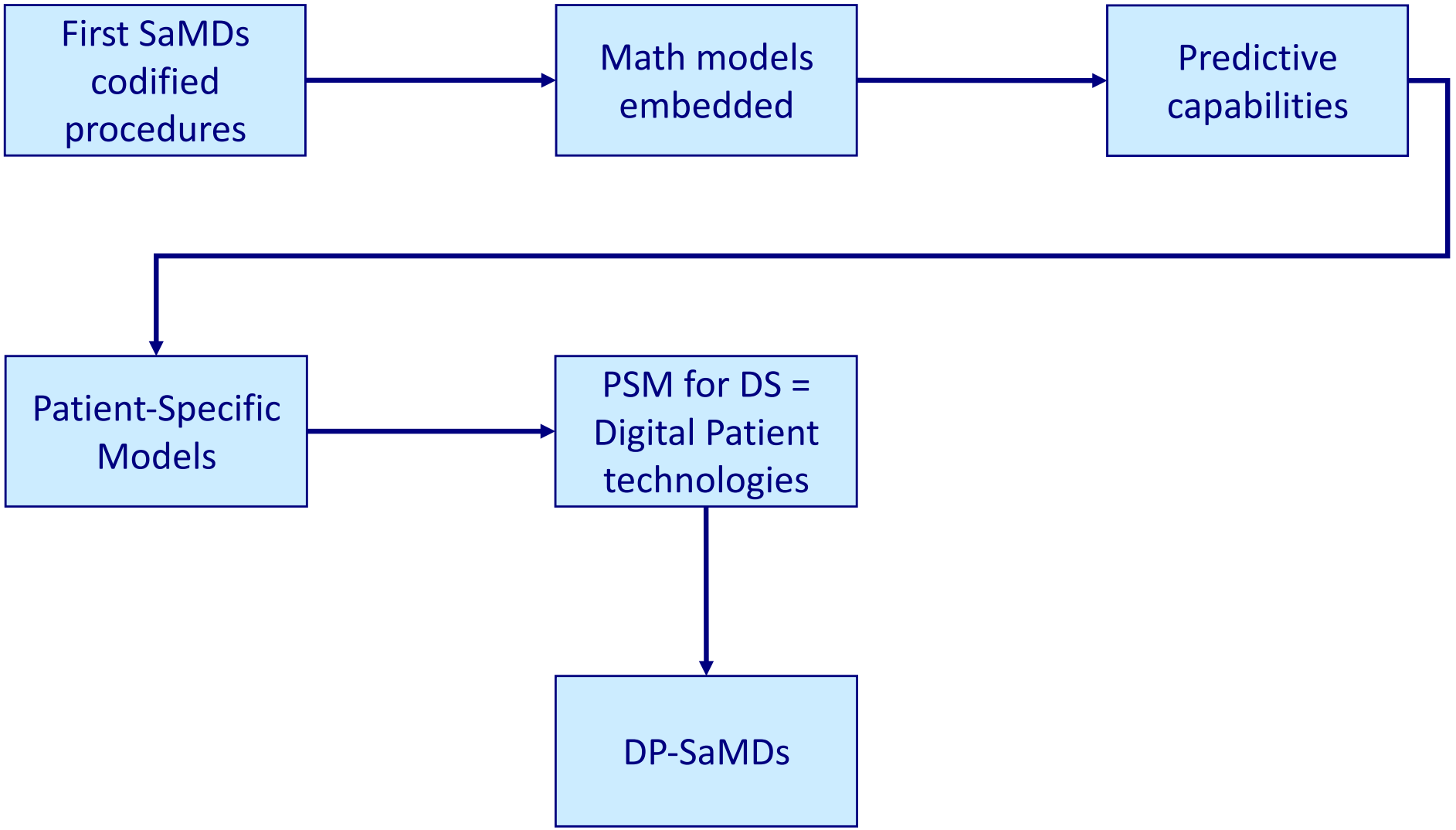
Diagram by Karn G. Bulsuk (http://www.bulsuk.com) CC BY-SA 3.0



Directive 93/42/EEC

Predictive software

Digital Patient Technologies

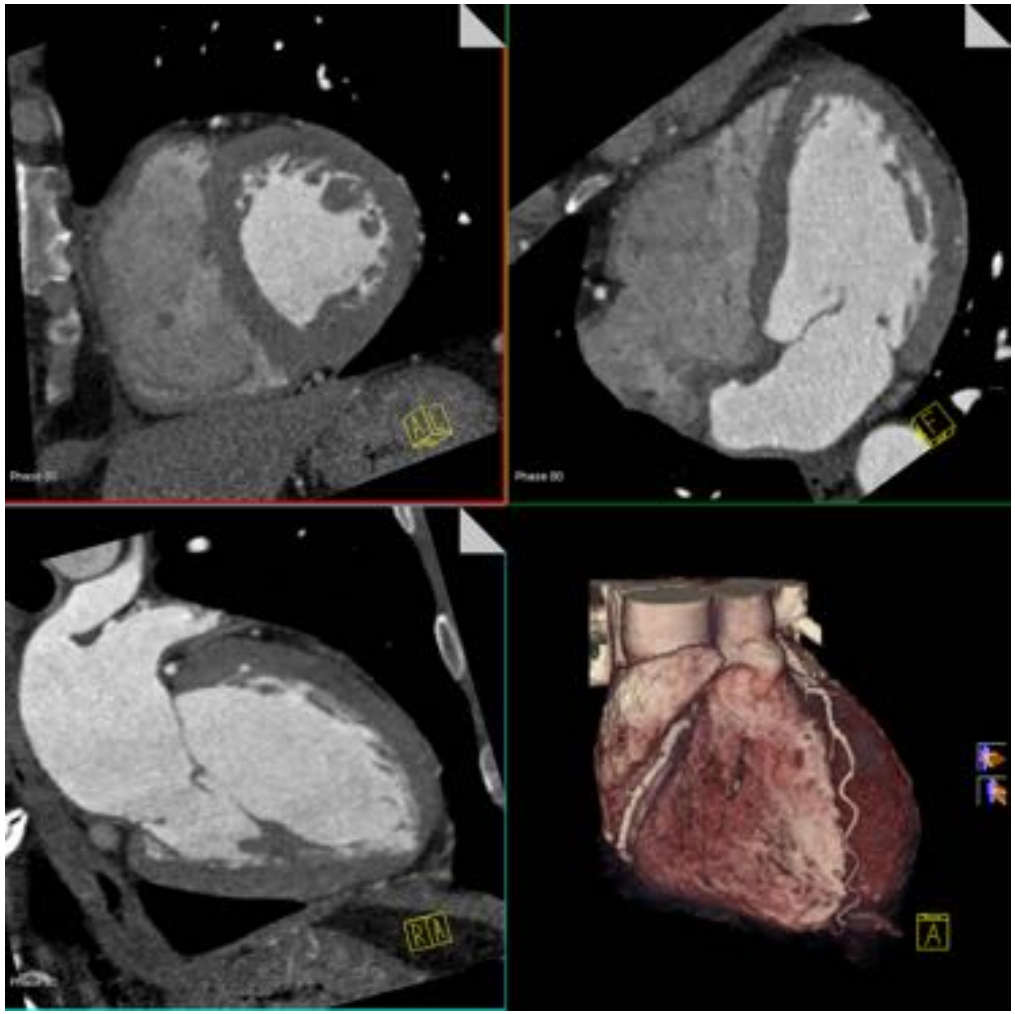


HeartFlow: first FDA DP-SaMD

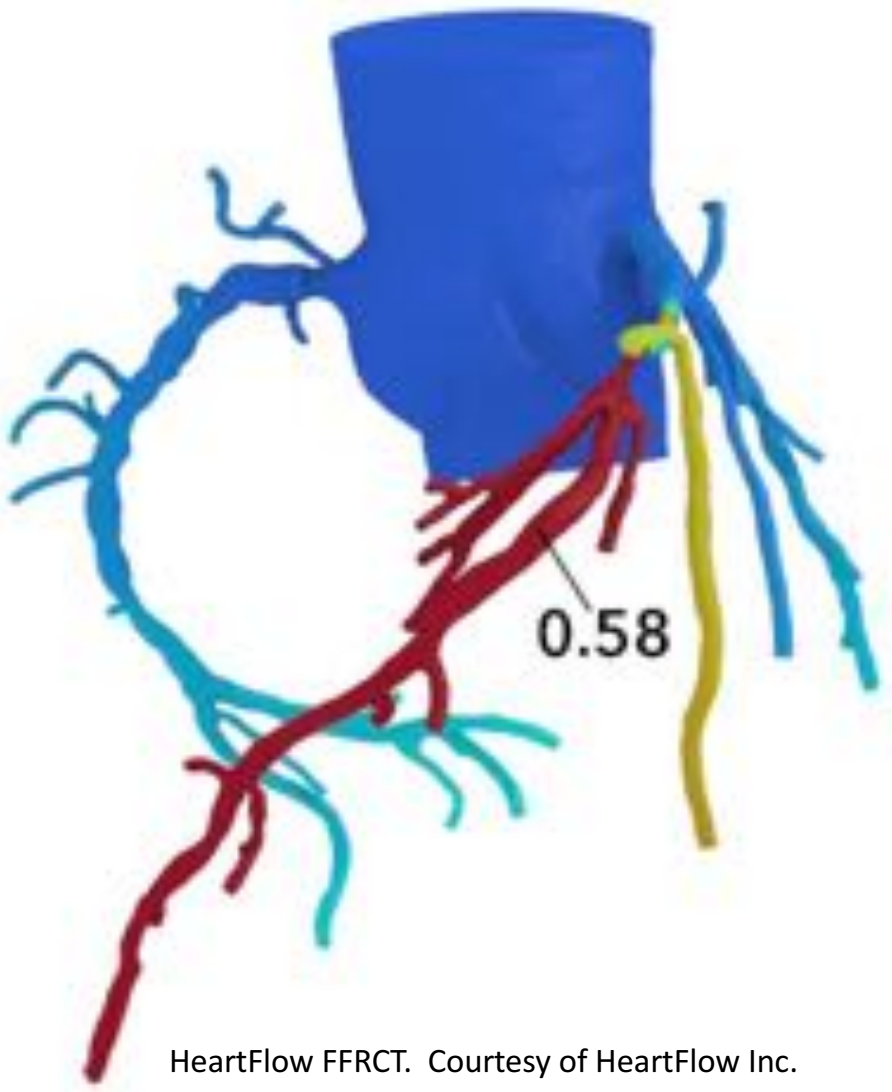
- On Nov 2014 the FDA approved, following a 513(f)(2)(De novo) pathways, the HeartFlow FFRCT software that predicts the fractional flow reserve (FFR) of a coronary stenosis from cardiac-CT images, using a patient-specific model
- The product belongs to a new Device Classification called “Coronary Vascular Physiologic Simulation Software”

HeartFlow: FFRCT

Coronary CT Angiography



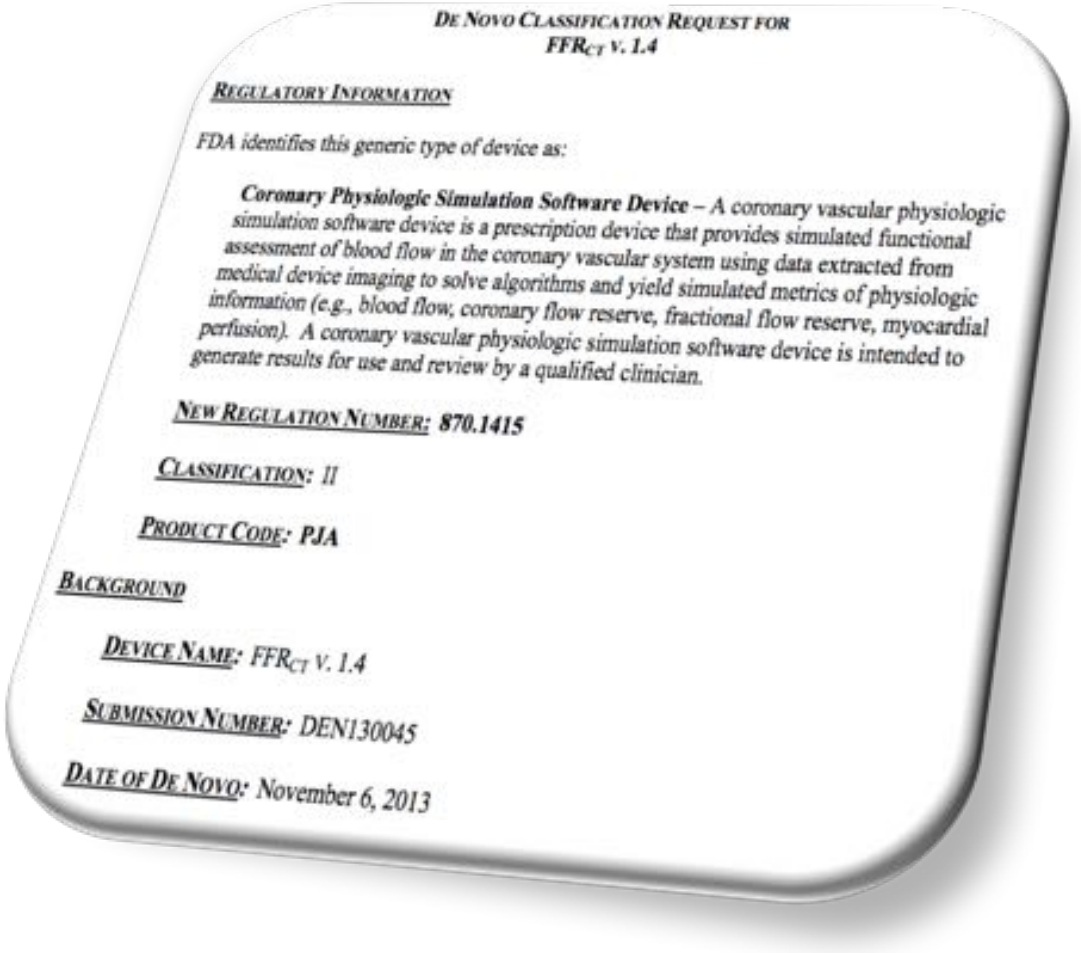
La Barbera M. Noninvasive Cardiac Imaging: Coronary CT Angiography
https://www.clinicalcorrelations.org/?p=679



HeartFlow FFRCT. Courtesy of HeartFlow Inc.

HeartFlow: De Novo pathway

- SW risk analysis
- Source data
- SW V&V
- Bench tests
- Human factors testing
- Animal testing not enough ➔ Clinical trials
- Consistency study
- HeartFlowNXT: 11 sites, 8 countries, 484 vessels FFR and CTFFR



DE NOVO CLASSIFICATION REQUEST FOR
FFR_{CT} V. 1.4

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Coronary Physiologic Simulation Software Device – A coronary vascular physiologic simulation software device is a prescription device that provides simulated functional assessment of blood flow in the coronary vascular system using data extracted from medical device imaging to solve algorithms and yield simulated metrics of physiologic information (e.g., blood flow, coronary flow reserve, fractional flow reserve, myocardial perfusion). A coronary vascular physiologic simulation software device is intended to generate results for use and review by a qualified clinician.

NEW REGULATION NUMBER: 870.1415

CLASSIFICATION: II

PRODUCT CODE: PJA

BACKGROUND

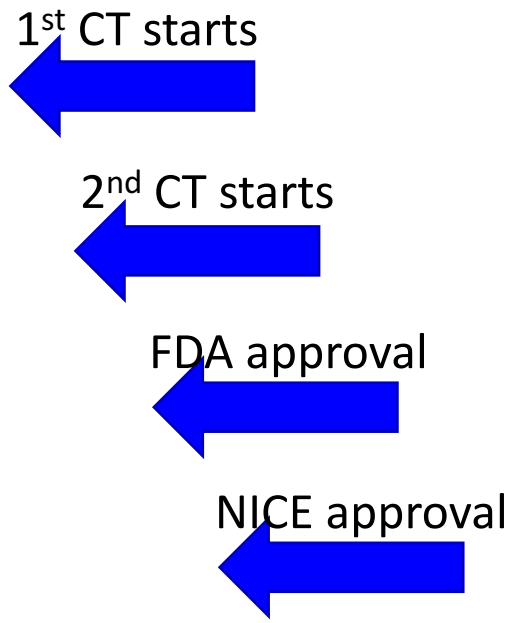
DEVICE NAME: FFR_{CT} V. 1.4

SUBMISSION NUMBER: DEN130045

DATE OF DE NOVO: November 6, 2013

HeartFlow: cash burning

Date	HeartFlow VC Funding
19/04/2010	$1,600,000.00
14/06/2010	$11,600,000.00
04/02/2011	$32,016,022.00
27/02/2014	$136,715,918.00
15/01/2016	$236,646,417.00

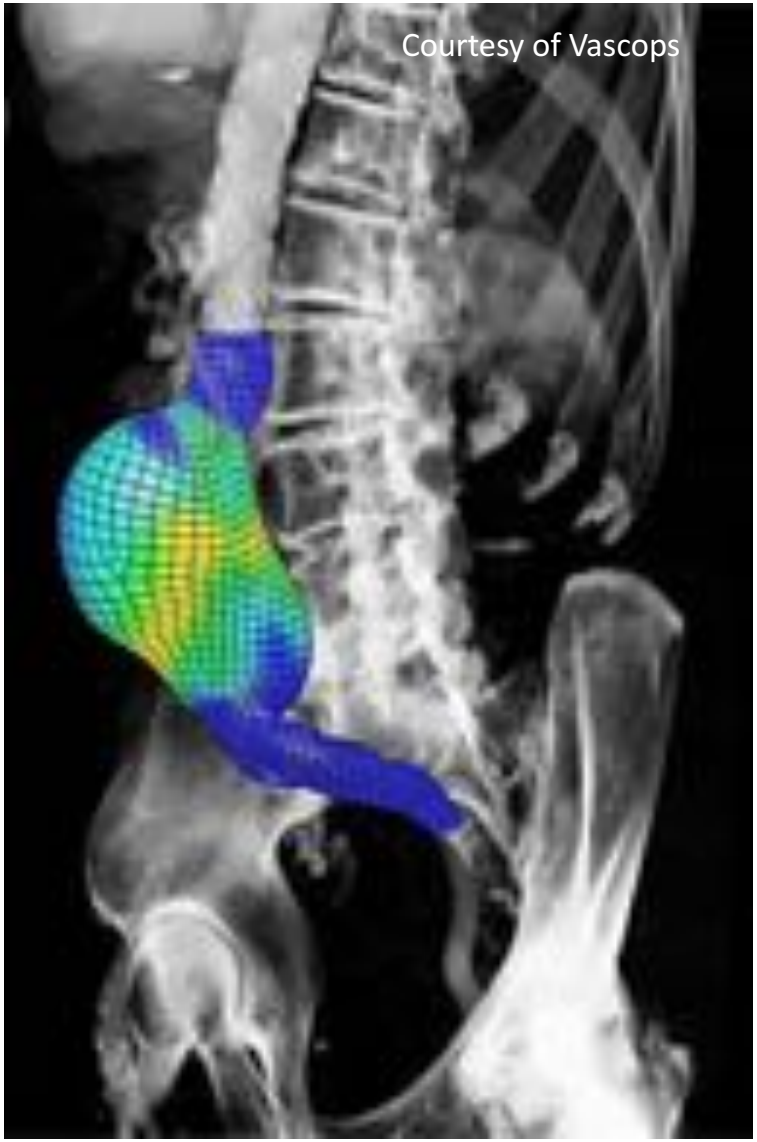


DP-SaMD: CE Marking

- Stand alone software that meets the definition of a medical device shall be considered as an active medical device. Decision Support Software is a SaMD (source: MEDDEV 2.1/6). It is all about risk classes:
  - Class I
    - orthopaedic planning software to measure interpedicular distance
  - Class IIa
    - Registration of PET datasets on CT datasets for follow-up tumour treatment
    - Software for the presentation of the heart rate during routine check-ups
  - Class IIb
    - radiotherapy planning system
    - insulin dosage planning stand alone software
    - Software for the presentation of the heart rate for intensive care monitoring
  - Class III
    - fractal dimension analysis for skin cancer
    - diagnostic image analysis for acute stroke

VASCOPS: first EC DP-SaMD

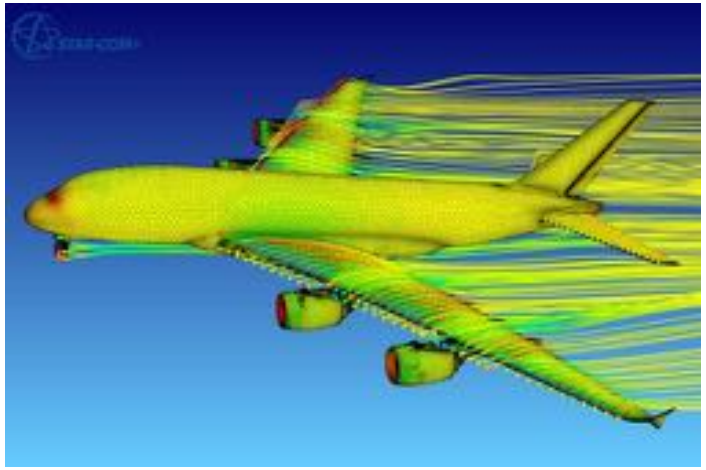
- Early screening of abdominal aortic aneurysm (AAA) patients
- Patient-specific risk assessment
- Automatic measuring device
- Translation of individual patients with respect to mean population data
- Certified as Class IIb medical device by PMG (Austria) (owned by Graz University of Technology)

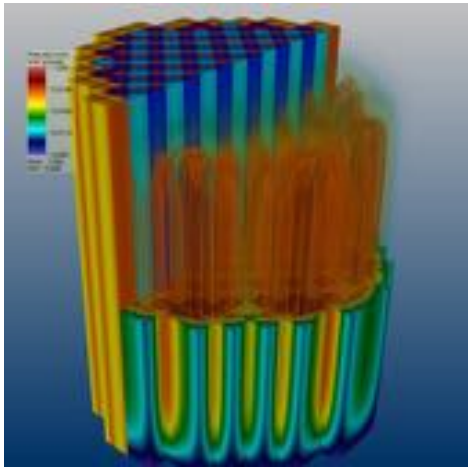


In silico clinical trials

The use of individualised computer simulation in the development or regulatory evaluation of a medicinal product or medical device/medical intervention

Modelling & simulation





The slow progression

1025 - Ibn Sīnā – Canon of Medicine

By Coffeetalkh (Own work) [CC BY-SA 3.0], via Wikimedia Commons

2015 – M&S not allowed

By Argonne National Laboratory's Flickr page
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Recommendations to regulators

16 July 2015

"the Committee urges FDA to engage with device and drug sponsors to explore greater use, where appropriate, of In Silico trials for advancing new devices and drug therapy applications" Senate Fiscal Year 2016 FDA Appropriations Bill (S. 1800) & Report (S. Rept. 114-82)

10 March 2016

"advances in alternative testing require the creation of a regulatory framework […] including for example the recognition and evaluation of modelling and simulation technologies". EU Parliament amendment to Regulation (EC) No 726/2004

In Silico Clinical Trials

"The use of individualised computer simulation in the development or regulatory evaluation of a medicinal product or medical device/medical intervention." **Avicenna Roadmap**

Modelling & Simulation technologies to reduce, refine, or partially replace both animal and human experimentation.

Terminology

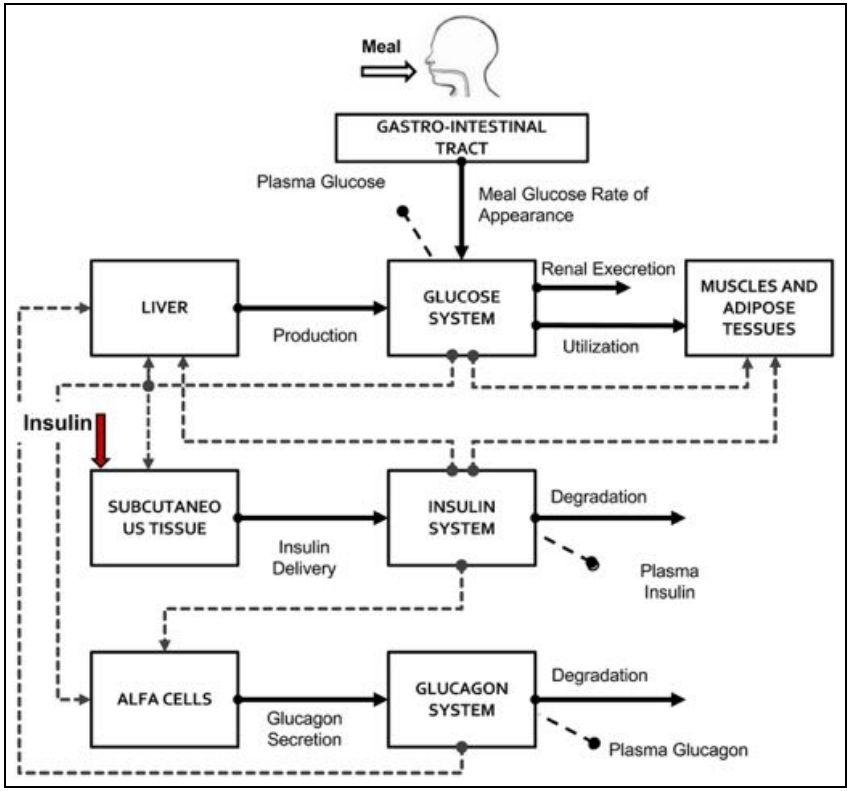
- **Reduce** the number of in vitro experiment, or animals enrolled, or of patients enrolled
- **Refine** the experiments to reduce the suffering (animals) or the risks (humans)
- **Replace** entirely the in vivo experiment
- **Improve** the ability of pre-clinical tests to predict the clinical outcome

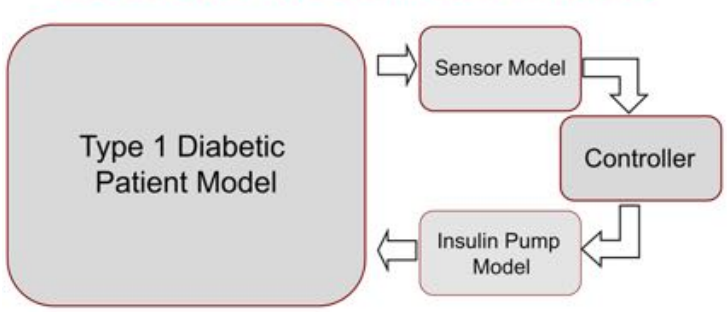
ISCT: A tentative taxonomy

- Pre-clinical
  - Discovery
  - Design
  - In vitro
    - Reduce, Replace
    - Improve
  - In vivo
    - Reduce, Refine, Replace
    - Improve
- Clinical
  - Reduce
  - Refine
  - Partially replace
    - To reduce cohort
    - To reduce duration
    - To sample tails
  - In silico-augmented
    - To reduce cohort
    - To reduce duration
    - To sample tails

UVA/Padua T1DM Simulator

- 2006: Juvenile Diabetes Research Foundation starts the Artificial Pancreas Project
- FDA requires algorithms to be tested on dogs before human trials are allowed
- UVA/Padua simulator virtual patients cohort includes 100 adults, 100 adolescents, and 100 children, spanning the variability of the T1DM population observed in vivo
- 2008: FDA approves investigational device exemption supported only by simulator results



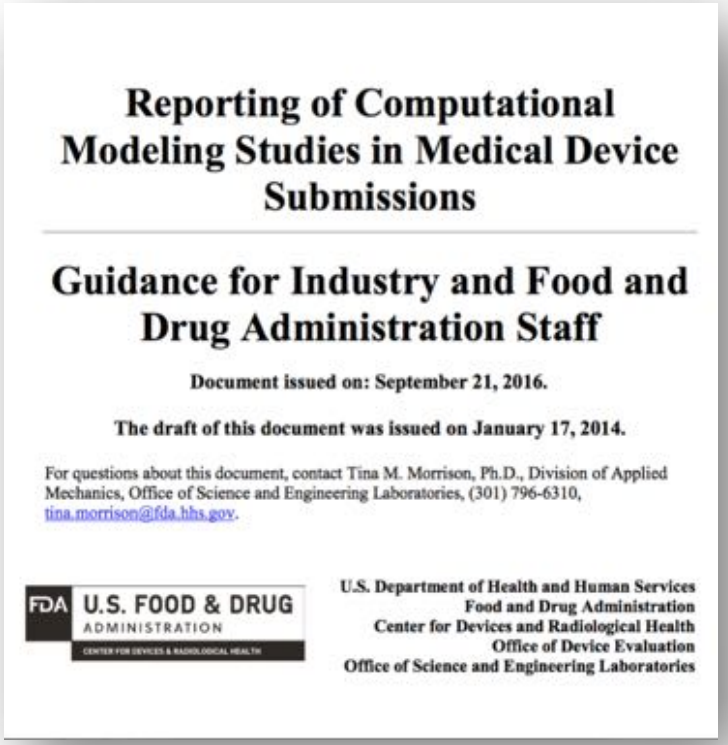


Where are we?

- No regulator has an established pathway yet
- All recommend a interactive approach
- USA Food & Drug Administration
  - Insistence on models credibility and validation linked to context of use
  - Engage with Modeling & Simulation WG @ Office of the Chief Scientist
  - Pursue mock submission to obtain informal feedbacks
  - Seek approval for modelling tools separately
- European Medicine Agency
  - Insistence on separating models of physiology, disease, and intervention
  - Engage with EMA Innovation Task Force
  - Pursue EMA Scientific advice (non binding)
  - Seek qualification for modelling tools separately

FDA Guidance on M&S use

- **Context of use** of the CM&S study including a clear identification of the quantity(s) of interest (QOI) (e.g., to determine the maximum stress value(s) and location(s))
- **Scope of the analysis** (e.g., for a device that has multiple sizes and/or configurations, specify which sizes and/or configurations were modeled, and how the computational model relates to the intended patient population)



Reporting of Computational Modeling Studies in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 21, 2016.

The draft of this document was issued on January 17, 2014.

For questions about this document, contact Tina M. Morrison, Ph.D., Division of Applied Mechanics, Office of Science and Engineering Laboratories, (301) 796-6310, tina.morrison@fda.hhs.gov.

FDA U.S. FOOD & DRUG ADMINISTRATION

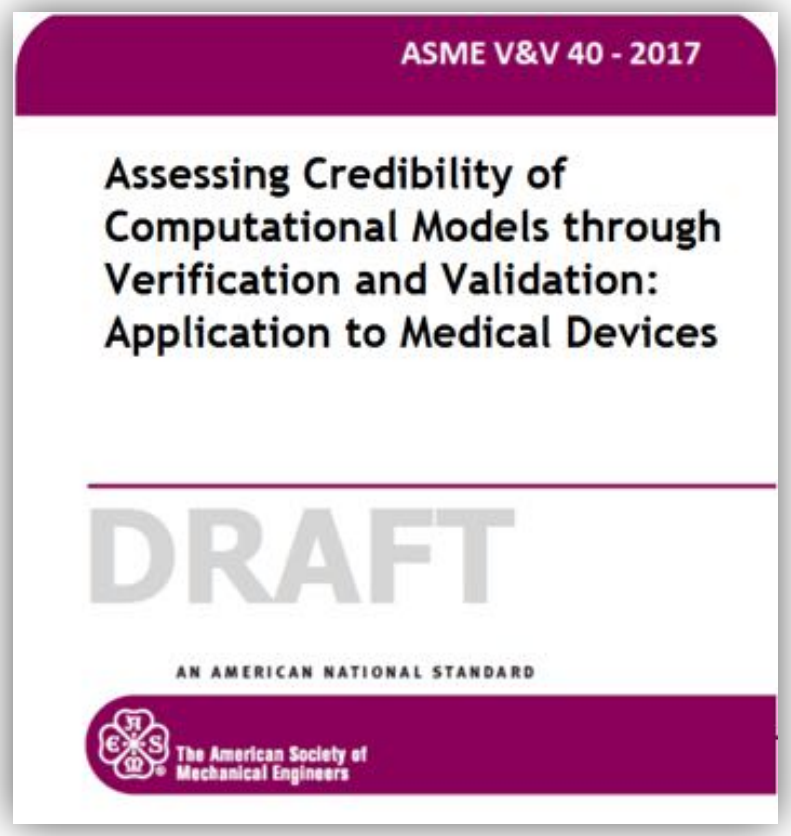
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Office of Science and Engineering Laboratories

- **Type of analysis** (e.g., fluid dynamics and mass transport, solid mechanics, electromagnetics and optics, ultrasound, heat transfer)
- **Conduct Verification, Validation & Uncertainty Quantification**
- **Conclusions** with respect to the context of use
- **Keywords**

ASME Committee V&V-40

- Scope: Verification and validation in computational modeling of medical devices

- Charter of V&V40: Coordinate, promote, and foster the development of standards that provide procedures for assessing and quantifying the accuracy and credibility of computational models and simulations



Comment period ends 23/1/2018

https://cstools.asme.org/csconnect/PublicReviewPage.cfm

Definitions

Verification	Did you solve the underlying mathematical model correctly?	Mathematical Evidence
Validation	Does the underlying mathematical model correctly represent the reality of interest?	Experimental Evidence
Uncertainty Quantification	What is the uncertainty in the inputs (e.g., parameters, initial conditions), and what is the resultant uncertainty in the outputs?	Statistical Evidence
Applicability	How relevant is the validation evidence to support using the model in the context of use?	Engineering Judgement
Credibility	Based on the available evidence, is there belief in the predictive capability of the computational model for the context of use?	Engineering Judgement

V&V-40: Credibility assessment

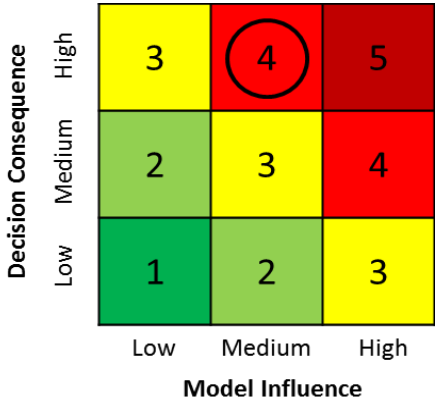
Purpose

Define Context of Use

Use the model to predict the outcome of ISO7206-4 on Ti6Al4V cementless hip stem

FEM model to predict peak cyclic stress, and form that predict the risk of fatigue fracture

Assess model risk



Prediction error <10% of fatigue limit

Establish credibility threshold

Establish VV&UQ plan

The winding road to credibility

Activities		Credibility Factors
Verification	Code	Software Quality Assurance
		Numerical Code Verification
	Calculation	Discretization Error
		Numerical Solver Error
		Use Error
Validation	Computational Model	Model Form
		Model Inputs
	Comparator	Test Samples
		Test Conditions
	Assessment	Equivalency of Input Parameters
		Output Comparison
Applicability		Relevance of the Validation to the COU
		Relevance of the Quantities of Interest

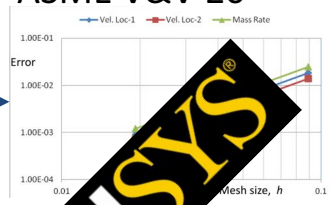
Adapted from V&V40 Document - Draft v11 – Public Comment (Fall 2017)

Verification

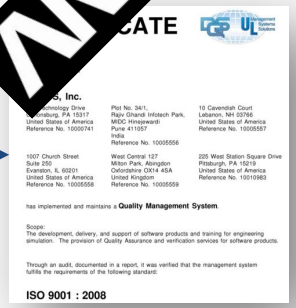
Numerical Code Verification

Software QA

ASME V&V-20

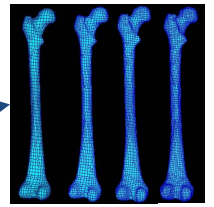


ANSYS®

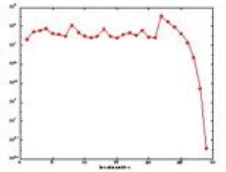


Code Verification

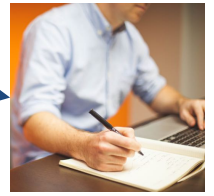
Discretisation error



Solver error



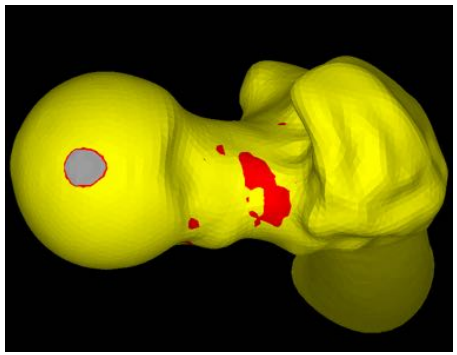
Use error
(Human)

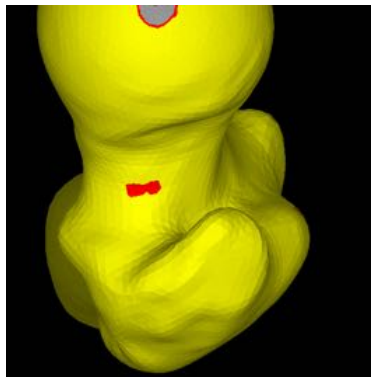


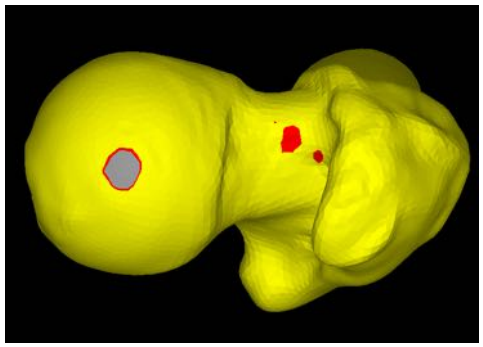
Calculation Verification

Validation

- Credibility factors
  - Model Form
    - governing equations
    - system configuration (i.e. geometry)
    - system properties (i.e. materials)
    - system conditions (i.e. loads)
  - Model Inputs
  - Comparator
    - In vitro, ex vivo, in vivo
  - Assessment





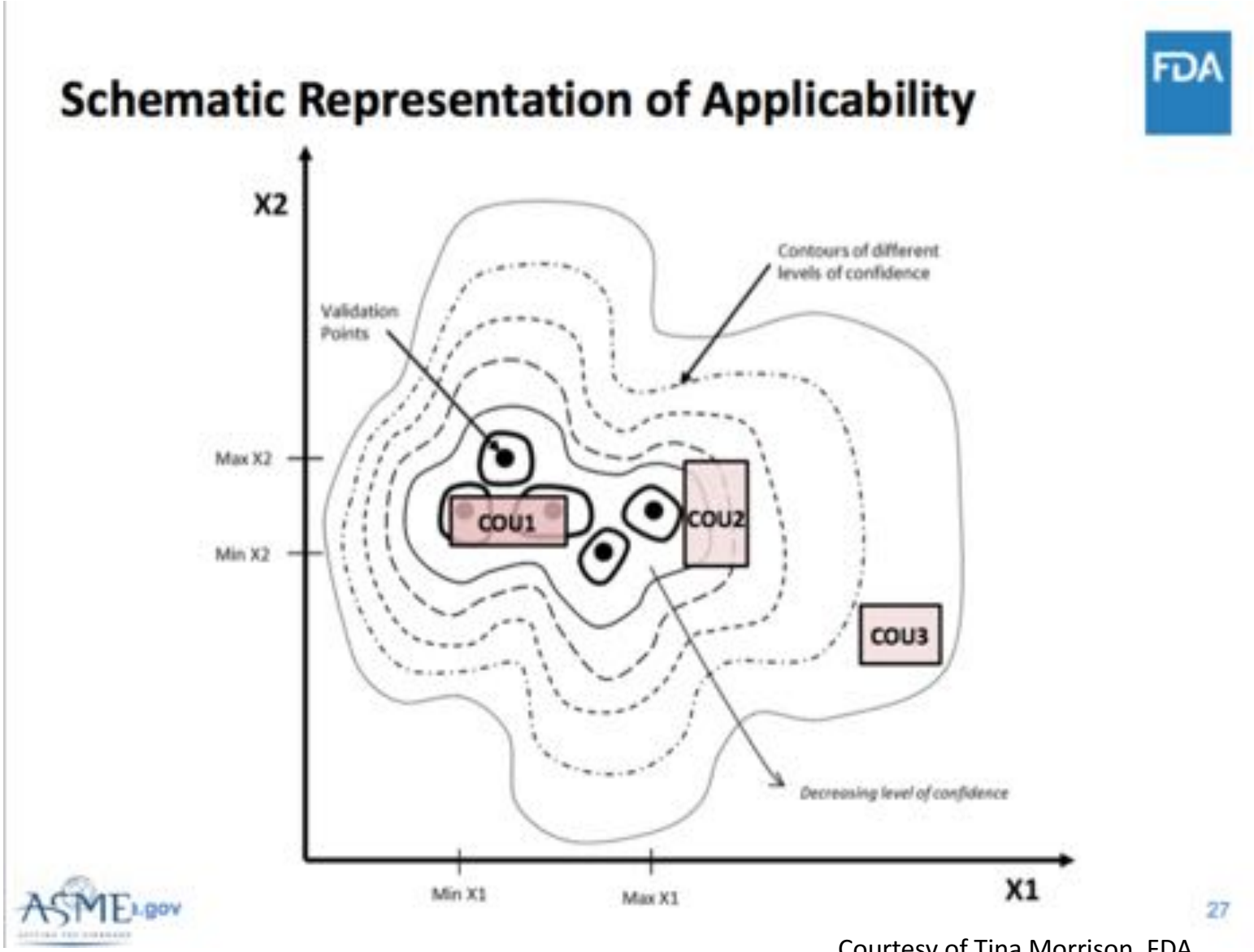



Assessment: output comparison

Level 1	Visual comparison concludes good agreement.
Level 2	Comparison by measuring the difference between computational results and experimental data. Differences are less than 20%.
Level 3	Comparison by measuring the difference between computational results and experimental data. Differences are less than 10%.
Level 4	Comparison with uncertainty estimated and incorporated from the comparator or computational model. Differences between computational results and experimental data are less than 5%. Includes consideration of some uncertainty, but statistical distributions for further uncertainty quantification are unknown.
Level 5	Comparison with uncertainties estimated and incorporated from both the comparator and the computational model, including comparison error. Differences between computational results and experimental data are less than 5%. Statistical distributions are known for rigorous treatment of uncertainty.

Adapted from V&V40 Document - Draft v11 – Public Comment (Fall 2017)

Applicability analysis



Courtesy of Tina Morrison, FDA

The winding road to credibility

Activities		Credibility Factors
Verification	Code	Software Quality A
		Numerical C
	Calculation	Discreti
		N
Validation	Computational M	
		nputs
	Com	st Samples
		Test Conditions
		Equivalency of Input Parameters
		Output Comparison
An		Relevance of the Validation to the COU
		Relevance of the Quantities of Interest

Ada Document - Draft v11 – Public Comment (Fall 2017)

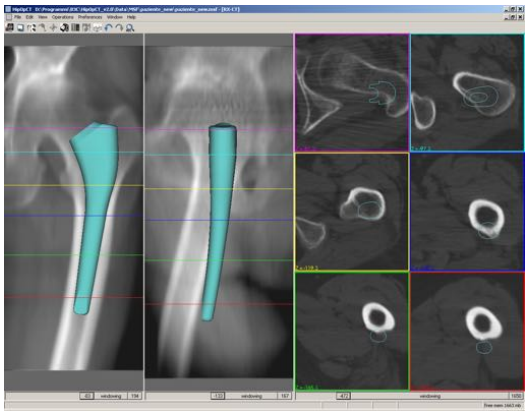
Credibility of the Analyst?

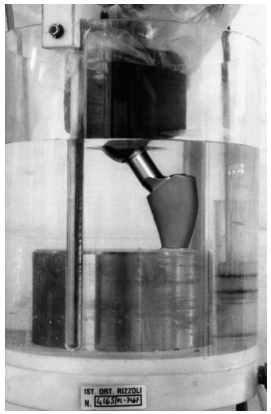
Specialists training

Conclusions

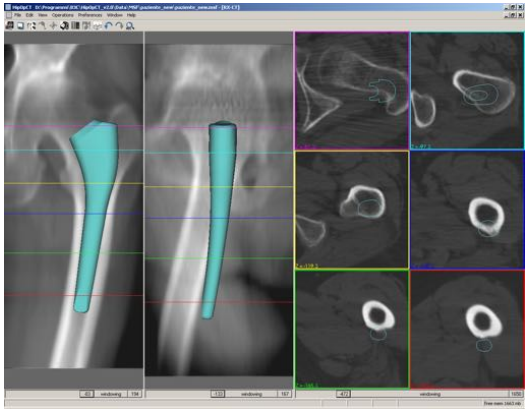
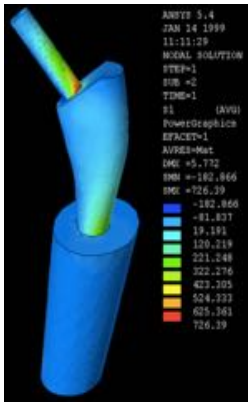
- In silico Medicine is turning from a researchers' dream into an industrial reality
- Software QA is a mature field
- SaMD regulatory pathways are stabilising, and should get simpler as more products are certified
- DP-SaMD certification remains challenging but one call follow the "First in Class"
- ISCT will transform the regulatory process for medical devices
- It will take a few years before the regulatory pathways are stable and mature enough
- As for all disruptive innovations, early adopters will harvest bigger benefits

The future: Personalised in silico




3 weeks


3 days

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