令和4年度第1回ISO/TC194国内委員会

WG1・7・15 の紹介

２０２２．４．１９

MTJAPAN 坂口圭介

WG1について

- WG名称： Systematic approach to biological evaluation and terminology
  （生物学的評価と用語への体系的なアプローチ）
  医療機器の生物学的安全性評価の国際調和した基本指針の作成

- 作成文書： ISO 10993-1
  Evaluation and testing within a risk management process
  （リスク管理プロセスにおける評価と試験）

- コンビーナ： James Anderson（米）

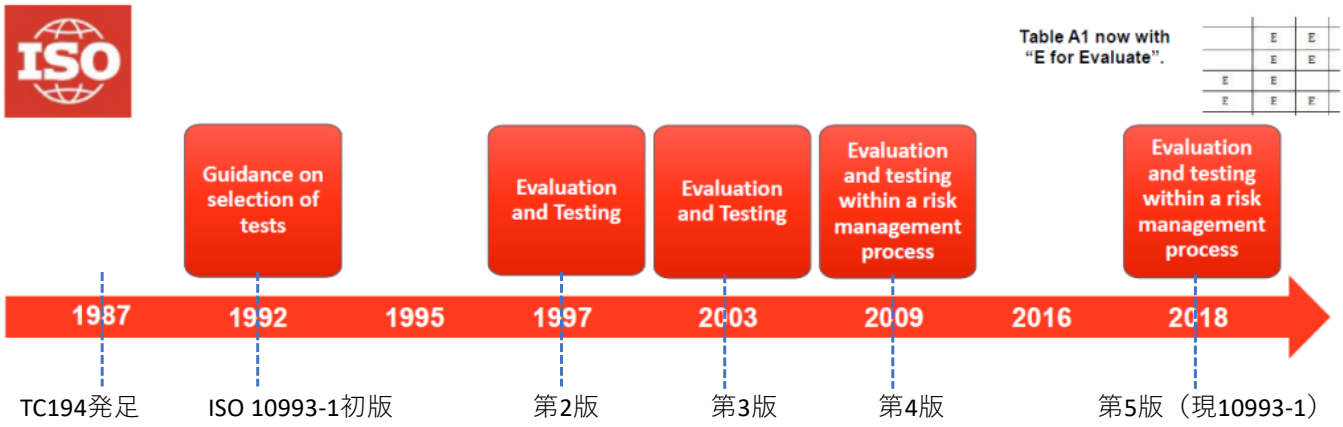
2021年より開始した改訂プロジェクトではArthur Brandwood（豪）がLeader

前回改訂は Jennifer Goode（FDA）とAnita Sawyer（BD）がco-convenorとして協力。

当該ISOの重要性から、国内委員会では委員長が主査、副委員長が副査を担当し対応してきた。

豪Arthur Brandwood氏の資料より

The Evolution of Part 1)



2021年度　WG1の動き

2021年5月：　豪よりISO 10993-1改訂の提案（N1187）→投票（5/31-8/21）

Target date: 36 months.

Project leader: Arthur Brandwood.　⇒　日本はコメント付き賛成投票

同　8月：　投票結果：Q.1: "Do you agree to start a revision of ISO 10993-1?"

22 x Yes、2 x No　（Germany 、US）、7 x Abstain

Q.2: "Do you have comments on the document (N 1187)?"

10 x Yes

Q.3 : "We nominate the following expert(s)."

7 x Yes、3 x New experts 、9 x Already nominated、

2022年1月：　オンラインミーティング　日本からは穴原・金澤・中岡・平井・森下・坂口が参加

豪による改訂趣旨と概略説明、独・米からの反対意見説明、議論

↓

改訂タスクチーム（10-15名）：1年後の本会議に向け2か月毎に進捗報告し改訂を進める

2022年度に向けたWG1今後の活動

Representation	Name
Chairman (AU)	Arthur Brandwood
WG1 Deputy Convenor (US)	Anita Sawyer
TC 194 Chair (UK)	Jeremy Tinkler
Secretariat (US, AAMI)	Jody Allen
Australia	Tim Moore
China	Chenghu Liu
Denmark	No delegate nominated – request CC of meeting papers.
Germany	Madlon Timme　(Alternate Klaus-Peter Stefan)
Ireland	Cathal Lucey,　Maire.NiDhomhnaill
Italy	Paolo Pescio
Japan	Ryusuke Nakaoka
Sweden	Monica Grekula
Switzerland	Philippe Hasgall
UK	Michelle Kelly
USA	Jennifer Goode,　Bob Przygoda

●改訂Task Groupは左記15名（2/21時点）

他のWGとの連携が必要となった場合には、そのconvenorsやexpertsを招聘し、議論を進めることになっている

●第一回TFミーティング

Scope から順に議論

3/29日本時間午後7時

（SOTとのバッティングのため、日程変更の可能性あり）

WG7について

- WG名称：Systemic toxicity　（全身毒性）
  医療機器の生物学的安全性評価における全身毒性評価法および関連毒性評価

- 作成文書：

ISO 10993-11：Tests for systemic toxicity（全身毒性の試験方法）2017年発行

ISO/TS 10993-20：　Principles and methods for immunotoxicology testing of medical devices　（免疫毒性試験の原則と試験方法）　2007年発行

- コンビーナ：　Daniel McLain（米）

- 国内主査･副査：　坂口　・　高島委員

当初Pyrogenicityも全身毒性としてWG7が担当していたが、2006年頃よりWG16としてWG7から分離。in vitro試験法（HCPTやエンドトキシン試験）を網羅した試験指針を作成した

WG15について

- WG名称：Strategic approach to biological assessment（生物学的評価の戦略的アプローチ）

  動物実験代替法など医療機器の生物学的安全性評価における全般的なトピック・課題・リエゾン報告を共有し議論して、担当WGの決定やWG間の調整を行う。（発足当時はTC194の幹部が運営していたが、近年は各WGのトピック等を発表して全体議論する場に変わっている）

- 作成文書： なし
- コンビーナ： Ed Reverdy（米）
- 国内主査・副査： 委員長 ・ 坂口

以下、関連資料

豪Arthur Brandwood氏の資料より

Why the revision?

- Better alignment with ISO 14971
- Fundamental review of some key parts

- ISO14971とのより良い整合
- 重要パートの基本的レビュー
  - Table A1/Evaluation process
  - Definitions
  - Annexes
  - Specific Technical Issues

独反対意見資料より

GERMAN COMMENTS ON RATIONALE FOR REVISION

DISAPPROVAL (only most relevant comments are mentioned)

- The actual working draft is not traceable why the number of categories is reduced to two groups. The reduction to two classes (not invasive and invasive medical device) will not increase the patient safety and will increase animal testing without additional evidence of risk, which is not in compliance with 3R.
- The nature of body contact (e.g. blood versus tissue) of the medical device is excluded in the update. There is no explanation provided, regarding the different risk of contact sites or their special risk.

- カテゴリを2つ（侵襲的および非侵襲的）に減らしても、患者の安全性は向上せず、動物実験が増えてしまう。
- 医療機器の身体接触部位（血液と組織など）が除外され、さまざまな固有リスクに関する説明が提供されていない。

米Anita Sawyerらの資料から

US FDA Negative Vote Summary	Comment Number(s)
The following proposals are inconsistent with US FDA regulatory requirements, and we are concerned this may cause confusion/inefficiencies for regulated industry and regulators: 1) Table 2: removal of device type clarification (i.e., not all devices in the new "invasive" categories will result in the same types of potential harms) 2) No requirements to start with a standardized approach, when TRA or testing is indicated	US-007, US-230, US-259, US-260, US-279, US-282, US-266, US-301, US-323, US-352, US-358
Emphasis on "materials" instead of "medical devices" and/or "medical device components" excludes impact of processing which can introduce toxicities. In addition, descriptions of "equivalence" and "partial equivalence" are not consistent with US FDA regulatory policy, and we are concerned will create confusion for regulated industry and regulators.	US-101, US-105, US-119, US-121, US-196, US-202, US-204, US-212, US-215, US-348
Improved text is needed on use of physical, chemical, and biological information to support risk assessment (not always a stepwise approach).	US-165, US-336, US-373, US-376
Clarification needed on determination of cumulative/repeat exposure for endpoint assessment.	US-242
Clarification needed on in vitro alternatives (including editorial comments that are not substantiated with device-relevant data) to include consideration of relevance of information.	US-047, US-189, US-211, US-322
Emphasis on chemistry/TRA, and biological testing as only options if potential harm is identified, is inconsistent with use of rationales and endpoints where geometry impacts on AEs (e.g., implantation, thrombogenicity) cannot be addressed by chemistry/TRA.	US-044

Request that all FDA comm *US-148, US-152, US-191, U*

WD提案は、米国FDAの規制要件と矛盾しており、規制対象の業界および規制当局に混乱/非効率を引き起こす可能性がある

Comparison of WD to Current 10993-1

(from PDF conversions to WORD and WORD Compare Tool on ISO 10993-1 2018 and ISO WD 10993-1 2021)
by Michael F Wolf

米Anita Sawyerらの資料から

Foreword **---- Comparisons to previous editions are deleted; statement of major changes made to existing standard not done**

Introduction **---- Substantial rewording**

1. Scope **---- Substantial rewording**

2. Normative references **---- Appropriate updating**

3. Terms and definitions ----

- **1 out of 26 -- NO CHANGE**
- **8 out of 26 -- CHANGED**
- **17 out of 26 -- DELETED**
- **6 new terms added**

4. General principles applying to biological evaluation of medical devices ----
Substantial revision with emphasis on applying a risk management framework according to ISO 14971 (also emphasized in new Table 1). Additional new material on Biological Evaluation Plan, Product Life Cycle, Biological Equivalence, Animal Welfare (the 3 Rs)

米Anita Sawyerらの資料から

Original Figure 1 on the Biological Evaluation process has been deleted:

Instead, a Risk Assessment flow chart, Figure 1, has been added

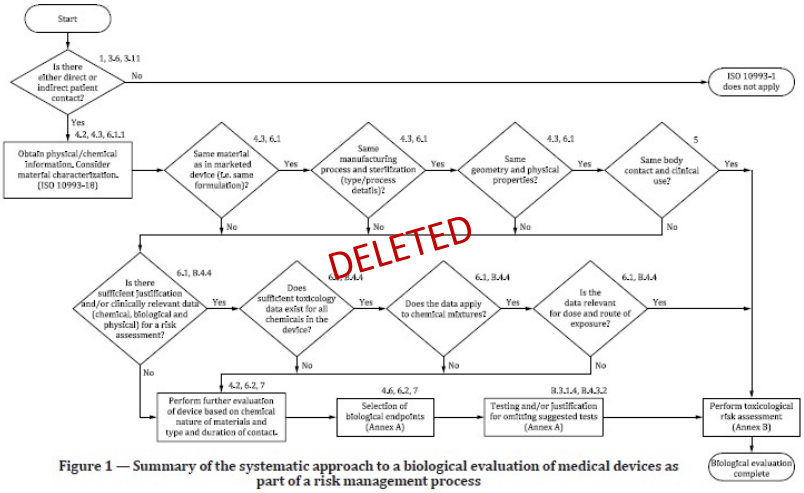
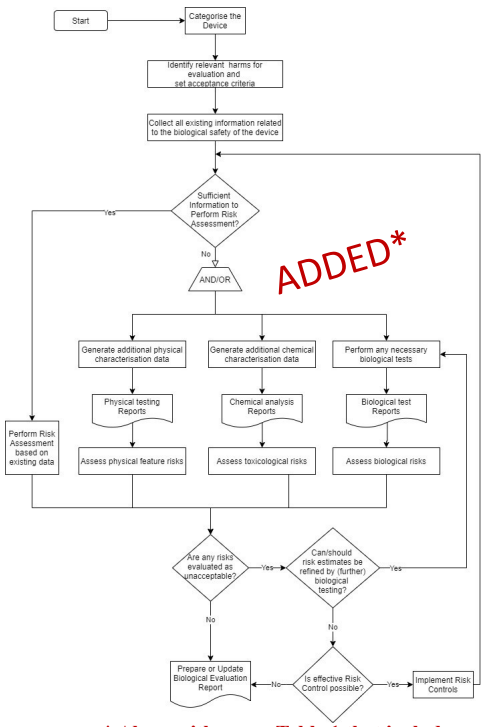


Figure 1 — Summary of the systematic approach to a biological evaluation of medical devices as part of a risk management process



*** Along with a new Table 1 that includes original Figure B1 from ISO14971**

5.3 Categorization by duration of contact ----Major revisions: addition of new *Table 2: Biological harms requiring evaluation according to device categorization*

米Anita Sawyerらの資料から

Table 2. Biological harms requiring evaluation according to device categorization

Body contact	Contact Duration	Cytotoxicity	Irritation	Sensitization	Systemic Toxicity: Pyrogenicity	Systemic Toxicity: Acute	Systemic Toxicity: Sub-Acute	Systemic Toxicity: Sub-Chronic	Systemic Toxicity: Chronic	Implantation effects	Genotoxicity	Carcinogenicity	Haemocompatibility
Intact Skin	All	E	E	E									NA
Invasive	<24h	E	E	E	E[1]	E[1]				E[4]	E[4]		All devices in contact with blood
	24h – 30d	E	E	E	E[1]	E	E			E[2]	E[3,4]		
	>30d	E	E	E	E[1]	E	E	E	E	E	E	E[3]	

ADDED

Table A.1 — Endpoints to be addressed in a biological risk assessment

Medical device categorization by: Nature of body contact	Contact duration	Endpoints of biological evaluation
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – Long-term (>30 d)
Surface medical device	Intact skin	A B C
	Mucosal membrane	A B C
	Breached or compromised surface	A B C
Externally communicating medical device	Blood path, indirect	A B C
	Tissue/bone/dentin	A B C
	Circulating blood	A B C
Implant medical device	Tissue/bone	A B C
	Blood	A B C

The above new Table 2 was simplified from the original Table A1