Are Cell Therapy Standards the Right Approach?

The Bioprocessing Summit, Boston 2019

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STANDARDS
Types

One issue is 'standards' cover a range of things, so its not always clear what people mean;

- Document standards (focus here)
  - Guidelines (range of sources, incl. regulators)
  - Pharmacopoeia monographs (chapters are guidance)
  - In-house SOPs etc
  - ISO, ASTM, etc (consensus standards)
  - Etc.
- Physical standards
  - WHO reference standards
  - Pharmacopoeia reference standards
  - In-house reference materials

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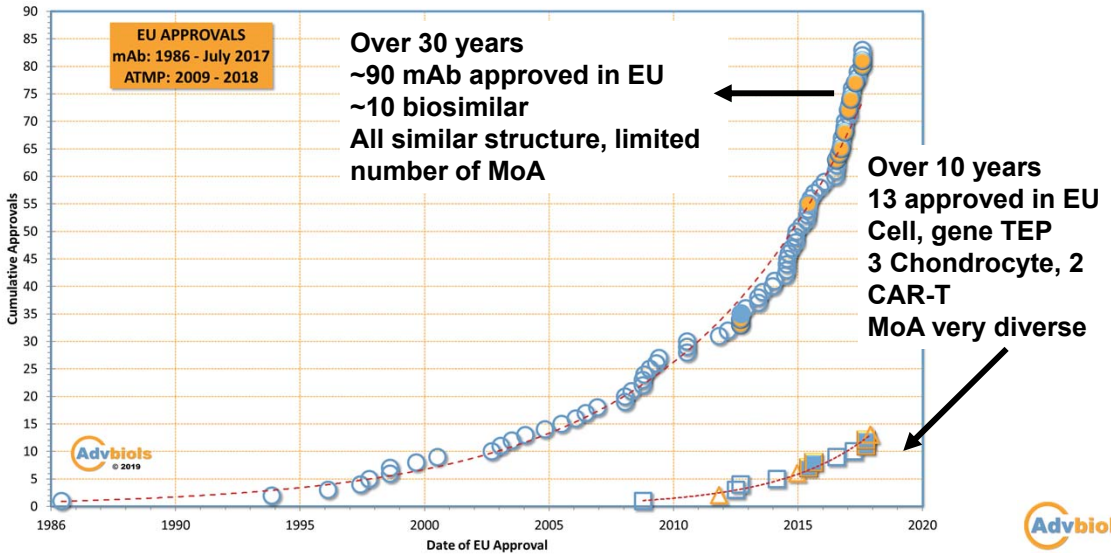
STANDARDS

Considering monoclonal antibodies



Web-search

- Basically nothing came up for document standards for mAbs
  - ISO, ASTM etc
- Quite a lot about reference standards for mAbs
  - Easier to understand why
  - Relates mostly to biosimilars

ISO STANDARDS

All the ISO documents for area = Biotechnology

ISO 20387:2018 Biotechnology -- Biobanking -- General requirements for biobanking		
ISO/CD TS 20388 [Under development] Biotechnology -- Biobanking -- Collection, processing, storage and trans biological material		
ISO 20391-1:2018 Biotechnology -- Cell counting -- Part 1: General guidance on cell countir		
ISO 20391-2 [Under development] Biotechnology -- Cell counting -- Part 2: Experimental design and statisti method performance		
ISO 20395:2019 Biotechnology -- Requirements for evaluating the performance of quanti target sequences -- qPCR and dPCR		
ISO/CD 20397-2 [Under development] Biotechnology -- General requirements for massive parallel sequencing quality of sequencing data		
ISO/TS 20399-1:2018 Biotechnology -- Ancillary materials present during the production of cel 1: General requirements		
ISO/TS 20399-2:2018 Biotechnology -- Ancillary materials present during the production of cel 2: Best practice guidance for ancillary material suppliers		
ISO/TS 20399-3:2018 Biotechnology -- Ancillary materials present during the production of cellular therapeutic products -- Part 3: Best practice guidance for ancillary material users	60.60	ISO/TC 276
ISO/DIS 20688-1 [Under development] Biotechnology -- Nucleic acid synthesis -- Part 1: Requirements for the production and quality control of synthesized oligonucleotides	40.60	ISO/TC 276
ISO/DIS 21709 [Under development] Biotechnology -- Biobanking -- Process and quality requirements for establishment, maintenance and characterization of mammalian cell lines	40.00	ISO/TC 276
ISO/DIS 21710 [Under development] Biotechnology -- Specification on data management and publication in microbial resource centers	40.00	ISO/TC 276
ISO/DIS 21899 [Under development] Biotechnology -- Biobanking -- General requirements for the validation and verification of processing methods for biological material in biobanks	40.60	ISO/TC 276
ISO/DIS 21973 [Under development] Biotechnology -- General requirements for transportation of cells for therapeutic use	40.00	ISO/TC 276
ISO/CD 23033 [Under development] Biotechnology -- Analytical methods - General guidelines for the characterization and testing of cellular therapeutic products	30.60	ISO/TC 276
ISO/CD TS 23105 [Under development] Biotechnology -- Biobanking -- Collection, processing, storage and transportation criteria for plant biological material	30.00	ISO/TC 276

ISO STANDARDS

Even pharmaceutical equipment has few

ICS	Field
11.120.01	Pharmaceutics in general
11.120.10	Medicaments *Including medical prescriptions and medicinal herbs*
11.120.20	Wound dressings and compresses
11.120.99	Other standards related to pharmaceutics *Including equipment for pharmaceutical industry*

Standard and/or project (9)	Stage	TC
ISO 11418-1:2016 Containers and accessories for pharmaceutical preparations -- Part 1: Drop-dispensing glass bottles	60.60	ISO/TC 76
ISO 11418-2:2016 Containers and accessories for pharmaceutical preparations -- Part 2: Screw-neck glass bottles for syrups	60.60	ISO/TC 76
ISO 11418-2:2016/Amd 1:2017	60.60	ISO/TC 76
ISO 11418-3:2016 Containers and accessories for pharmaceutical preparations -- Part 3: Screw-neck glass bottles (veral) for solid and liquid dosage forms	60.60	ISO/TC 76
ISO 11418-3:2016/Amd 1:2017	60.60	ISO/TC 76
ISO 11418-4:2005 Containers and accessories for pharmaceutical preparations -- Part 4: Tablet glass bottles	90.20	ISO/TC 76
ISO 11418-5:2015 Containers and accessories for pharmaceutical preparations -- Part 5: Dropper assemblies	60.60	ISO/TC 76
ISO 11418-7:2016 Containers and accessories for pharmaceutical preparations -- Part 7: Screw-neck vials made of glass tubing for liquid dosage forms	60.60	ISO/TC 76
ISO 21976:2018 Packaging -- Tamper verification features for medicinal product packaging	60.60	ISO/TC 122

STANDARDS
Why are there few/no consensus standards for mAbs?

- All biological medicinal products (biologics) are inherently different (as are biological raw materials)
  - Most are new active substances, so unique
  - But even biosimilars (and me-too) have a different process (no /little knowledge of innovator process)
- The process is different for each (and proprietary) and influences;
  - Process-related impurities
  - Product-related impurities
  - And also prost-translational modifications can differ, e.g. glycosylation (proteins)
  - for cell therapy we can assume a bigger impact

STANDARDS
Biosimilars

- There are a few monographs for biotech (protein) active substances, e.g. erythropoietin, insulin
- Some argue (myself included) these are not useful
  - Because of previous slide (they are incomplete), need to be case-by-case
  - Not how you establish biosimilarity (some have made this mistake)
  - Not needed for me-too as they do full development (just like a new active substance)
- Suggests standards for the cellular active should not be attempted.

Note: the idea of a biosimilar cell therapy is currently implausible scientifically, and likely completely impractical or impossible (autologous).

STANDARDS
What standards might be useful?

Materials

- Standards for biological materials are (previous slides) unlikely to be very helpful
- Not many chemical materials that don't have a monograph.

STANDARDS
What standards might be useful?

Analytical Methods

- Pharmacopoeia monographs need to be validated methods (inter/intra lab), which is challenging given the diversity of samples that might be tested.
  - Potency is product and indication specific – so not possible.
  - Bioassays in general are unlikely to be suitable for a monograph
  - Cell counting seems deceptively simple, yet isn't amenable to this approach (cell type, matrix etc).
- Leaves guideline approaches (flexible)
  - Which is mostly where we are now, the developer has to develop and validate their methods.

STANDARDS
Often get misused.

International Society for Cellular Therapy ISCT

Cytotherapy (2006) Vol. 8, No. 4, 315–317

Taylor & Francis

POSITION PAPER

Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement

M Dominici[1], K Le Blanc[2], I Mueller[3], I Slaper-Cortenbach[4], FC Marini[5], DS Krause[6], RJ Deans[7], A Keating

[1]Laboratory of Cell Biology and Advanced Cancer Therapy, Oncology-He
Italy, [2]Center for Allogeneic Stem Cell Transplantation, Department of La

Cell Stem Cell
Forum

MSC-Based Product Characte
for Clinical Trials: An FDA Pers

Michael Mendicino,[1,2,*] Alexander M. Bailey,[3] Keith Wonnacott,[2] Ra
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Hampshire Boulevard, Silver Spring, MD 20993, USA
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http://dx.doi.org/10.1016/j.stem.2014.01.013

"In their 2006 position paper, ISCT emphasized that their proposed identifying criteria were not to be confused with final product lot release specifications developed for clinical trials (Dominici et al., 2006). Interestingly, literature and regulatory submission descriptions appear to indicate that many researchers believe otherwise."

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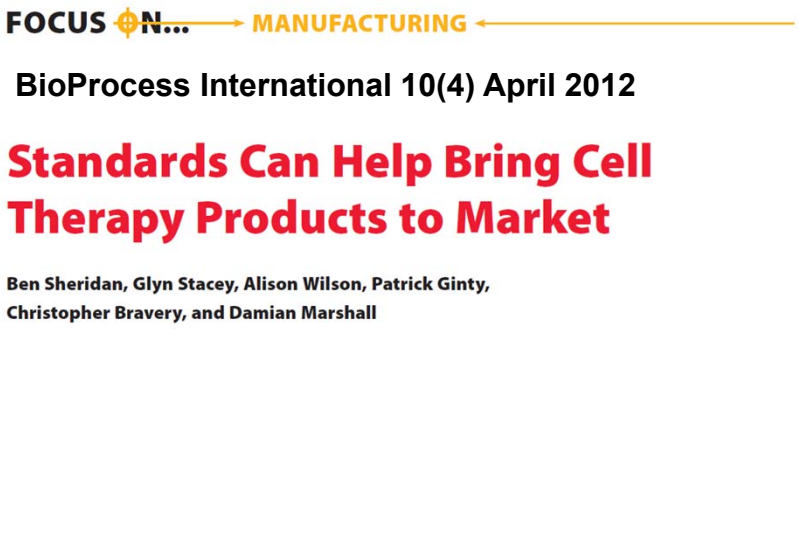
STANDARDS
Just to clarify, I do appreciate the potential value of standards.



FOCUS ON... MANUFACTURING

BioProcess International 10(4) April 2012

Standards Can Help Bring Cell Therapy Products to Market

Ben Sheridan, Glyn Stacey, Alison Wilson, Patrick Ginty, Christopher Bravery, and Damian Marshall

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THANK YOU FOR LISTENING

Questions?