CMC Strategy Forum Japan 2023
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U.S. FOOD & DRUG ADMINISTRATION

Center for Biologics Evaluation and Research (CBER) Updates

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CBER Products

- Gene therapies
- Human tissues and cellular products
- Xenotransplantation products
- Allergenics
- Live biotherapeutic products
- Vaccines (preventative and therapeutic)
- Whole blood, plasma, and blood products
- Devices related to biologics

Highlights

1. COVID-19 learnings and pathways for access
2. Establishing an annual framework for COVID-19 vaccines
3. Further progress on Cell and Gene therapy for rare diseases
4. Effectively stand up the Office of Therapeutic Products
5. Efforts supporting digitalization of regulatory submission

COVID-19 Learnings

- Expediting medical product development
- Facilitating adequate manufacturing capacity
- Ensuring early access to medical products
- Optimizing work with partially remote workforce

Bottlenecks Encountered

- Raw materials
- Disposable supplies
- Bioreactor capacity
- Fill finish capacity
- Skilled workforce
- Process development and scale-up of manufacturing

Use of Varied Pathways for Access

- Investigational New Drug Application (IND)
  - Research IND
  - Expanded access
- Biologics License Application (BLA)
  - Traditional (full) approval
  - Accelerated approval
  - Animal rule approval
- Emergency Use Authorization (EUA)

Conditions for Expanded Access

- Patient has a serious disease or condition, or whose life is immediately threatened by their disease or condition
- There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition
- Patient enrollment in a clinical trial is not possible
- Potential patient benefit justifies potential risks of treatment
- Providing the investigational medical product will not interfere with medical product's development

Emergency Use Authorization (EUA)

- Put in place after 9/11 to ensure that potentially lifesaving medical products could be available to people in medical need when there is not an approved and available alternative
- The standard used is that the product “may be effective” and its “known and potential benefits outweigh the known and potential risks

EUA Considerations for Vaccines That Will Be Deployed Widely

- Careful evaluation of quality, safety, efficacy
- Public advisory committee meeting
- Must demonstrate clear and compelling efficacy in a large well-designed phase 3 clinical trial
- Enhanced post-deployment surveillance

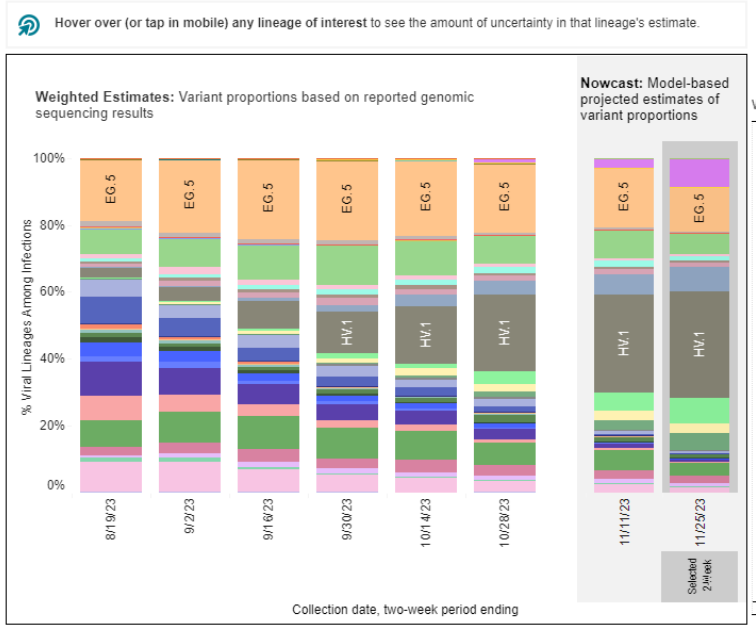
Emergency Use Authorization (EUA)

- Flexibility
  - Can adapt to the specific nature of the threat
- Adaptability
  - Can appropriately apply to different product classes
- Agility
  - Changes can be made rapidly as data emerge

Recent Evolution of SARS-CoV-2

Weighted and Nowcast Estimates in United States for 2-Week Periods in 8/6/2023 – 11/25/2023

Nowcast Estimates in United States for 11/12/2023 – 11/25/2023



USA

WHO label	Lineage #	%Total	95%PI
Omicron	HV.1	31.7%	28.3-35.2%
	EG.5	13.1%	11.8-14.7%
	BA.2.86	8.8%	4.8-15.2%
	JD.1.1	7.7%	5.8-10.0%
	HK.3	7.4%	6.0-9.1%
	FL.1.5.1	6.4%	5.4-7.6%
	JG.3	5.3%	3.7-7.5%
	XBB.1.16.6	4.0%	3.2-5.0%
	JF.1	2.8%	2.2-3.5%
	XBB.1.16.11	2.0%	1.4-2.7%
	XBB.2.3	1.8%	1.4-2.5%
	GK.1.1	1.4%	1.1-1.9%
	HF.1	1.4%	0.9-2.0%
	XBB.1.5.70	1.1%	0.5-2.4%
	XBB.1.16.15	1.0%	0.7-1.5%
	XBB.1.16	0.7%	0.5-1.0%
	XBB	0.6%	0.5-0.8%
	GE.1	0.6%	0.4-0.9%
	XBB.1.16.1	0.4%	0.3-0.6%
	GK.2	0.4%	0.3-0.6%
	EG.6.1	0.3%	0.2-0.4%
	XBB.1.9.1	0.2%	0.1-0.3%
	XBB.1.5	0.2%	0.1-0.2%
	CH.1.1	0.1%	0.1-0.2%
	XBB.1.5.68	0.1%	0.1-0.2%
	XBB.1.42.2	0.1%	0.1-0.2%
	XBB.1.9.2	0.1%	0.0-0.1%
	XBB.1.5.72	0.1%	0.0-0.1%
	XBB.2.3.8	0.1%	0.0-0.2%
	XBB.1.5.10	0.0%	0.0-0.0%
	XBB.1.5.59	0.0%	0.0-0.0%
	FD.1.1	0.0%	0.0-0.0%
	XBB.1.5.1	0.0%	0.0-0.0%
	EU.1.1	0.0%	0.0-0.0%
	FE.1.1	0.0%	0.0-0.0%
Other	Other*	0.1%	0.0-0.2%

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one 2-week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all 2-week periods displayed.
# BA.1, BA.3, BA.2.86 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. Except BA.2.12.1, BA.2.75, XBB and their sublineages, BA.2 sublineages are aggregated with BA.2. Except BA.2.75.2, CH.1.1 and BN.1, BA.2.7 sublineages are aggregated with BA.2.75. Except BA.4.6, sublineages of BA.4 are aggregated to BA.4. Except BF.7, BF.11, BA.5.2.6, BQ.1 and BQ.1.1, sublineages of BA.5 are aggregated to BA.5. Except the lineages shown and their sublineages, sublineages of XBB are aggregated to XBB. Except XBB.1.5.1,XBB.1.5.10,FD.2,EU.1.1,XBB.1.5.68 and XBB.1.5.70 sublineages of XBB.1.5 are aggregated to XBB.1.5. Except FL.1.5.1, sublineages of XBB.1.9.1 are aggregated to XBB.1.9.1. Except XBB.1.16.1,XBB.1.16.11,XBB.1.16.15 sublineages of XBB.1.16 are aggregated to XBB.1.16, sublineages of XBB.1.42.2 are aggregated to XBB. Except FE.1.1, sublineages of XBB.1.16.1 are aggregated to XBB. For all the other lineages listed, their sublineages are aggregated to the listed parental lineages respectively. Previously, FL.1.5.1, GE.1, EG.6.1 and HV.1, FD.1.1, XBB.2.3.8, HF.1, GK.2, GK.1.1, HK.3, JD.1.1, JF.1, JG.3 was aggregated to XBB.1.9.1, XBB.2.3.10, XBB.1.9.2, XBB.1.5.15, XBB.2.3, XBB.1.16.13, XBB.1.5.70, XBB.1.9.2.5.1.1, XBB.1.5.102, XBB.1.16.6 and XBB.1.9.2.5.1.3 respectively. Lineages BA.2.75.2, XBB, XBB.1.5 , XBB.1.5.1, XBB.1.5.10, FD.2, XBB.1.9.1, XBB.1.9.2, XBB.1.16, XBB.1.16.1, XBB.2.3, BN.1, BA.4.6, BF.7, BF.11, BA.5.2.6 ,BQ.1.1, EU.1.1, XBB.1.5.68, FE.1.1, EG.5, XBB.1.5.72 , FL.1.5.1, GE.1, EG.6.1,XBB.1.16.11, FD.1.1, XBB.1.5.70, XBB.2.3.8, HV.1, XBB.1.42.2, GK.2, HF.1, XBB.1.16.15, GK.1.1, HK.3, JF.1, JG.3, BA.2.86 contain the spike substitution R346T.

https://covid.cdc.gov/covid-data-tracker/#variant-proportions

Simplification of the COVID-19 Vaccination Regimen

General Population (age-based; one dose)*	Risk-based adjustments (dose(s) and schedule to be determined) **
Most individuals	**Persons with compromised immunity**
Young children *who have been previously immunized*	**Young children** *who have not been previously immunized*

*Presumed to have had sufficient S protein exposures such that a single dose of COVID-19 vaccine induces or restores vaccine effectiveness

**Presumed to have insufficient preexisting immunity based on age and other risks (e.g., young children who have not been previously immunized, older adults who have higher-level risk for severe COVID-19 and death, and persons with compromised immunity); may require more than one dose of vaccine in each COVID-19 vaccination campaign, doses and schedule to be determined

PROGRESS ON CELL AND GENE THERAPY FOR RARE DISEASES

U.S. Approved Gene Therapies

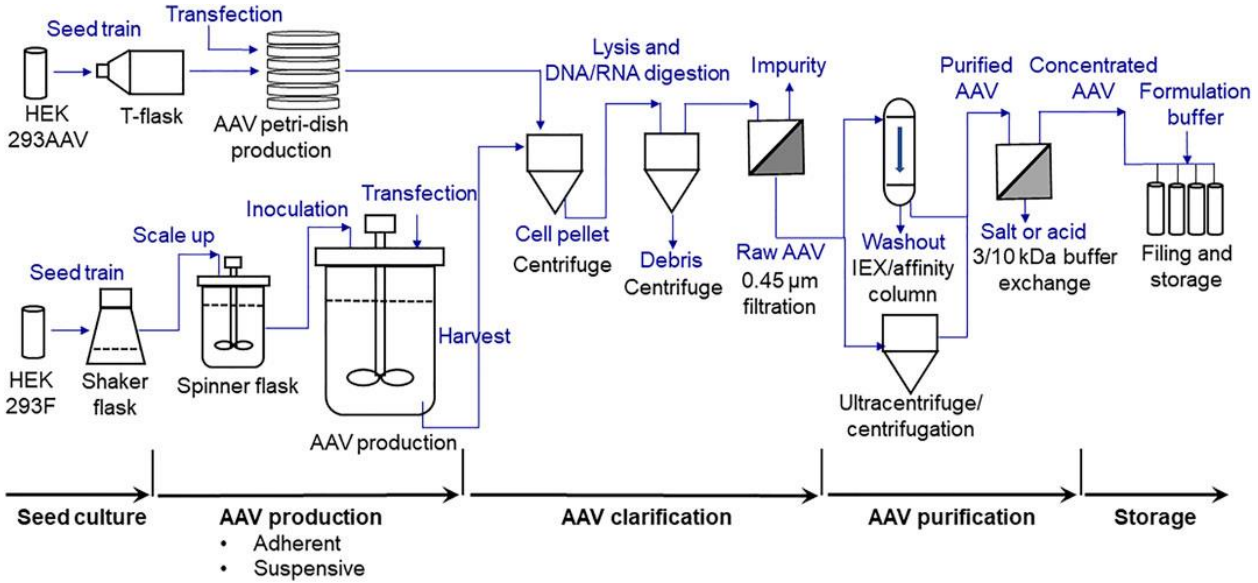
- Kymriah (2017)
- Yescarta (2017)
- Luxturna (2017)
- Zolgensma (2019)
- Tecartus (2020)
- Breyanzi (2021)
- Abecma (2021)
- Carvykti (2022)
- Zynteglo (2022)
- Skysona (2022)
- Hemgenix (2022)
- Adstiladrin (2022)
- Vyjuvek (2023)
- Elevidys (2023)
- Roctavian (2023)

Stem cell T cell Directly administered

Current Challenges

- Gene therapy is now at a critical juncture financially due to a combination of factors
  - Manufacturing challenges
  - Clinical development timelines
  - Different global regulatory requirements

Automating Vector Production



Guan G-S et al. Process Improvement of Adeno-Associated Virus Production. Chem. Eng., 28 January 2022 Sec. Biochemical Engineering https://doi.org/10.3389/fceng.2022.83042

Future of Manufacturing?

Will the gene therapy manufacturing platform of the future be a vector fabrication device?

Actions at Center for Biologics

- Advancing manufacturing technologies for cell and gene therapy through research
- Work to more clearly define the use of accelerated approval for gene therapy
- Exploring concurrent submission and product review with other regulatory authorities
- Operation Warp Speed for Rare Diseases
- Communication and CDRP pilots

Communications Pilot

Leveraging Learnings from Operation Warp Speed

- Background: experience with COVID-19 product development indicated the potential benefits of frequent communication
- Purpose: further accelerate the pace of development of therapeutics for small populations with high medical need
- Products eligible: products for life-threating rare genetic diseases showing promising efficacy early in development
- Procedures: initial meeting followed by ongoing informal interactions via email or live meetings on an as needed basis

CMC Development and Readiness Pilot Program (CDRP)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2022–N–2396]

Chemistry, Manufacturing, and Controls Development and Readiness Pilot Program; Program Announcement

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the opportunity for a limited number of applicants to participate in a Chemistry, Manufacturing, and Controls (CMC) Development and Readiness Pilot (CDRP) program, to facilitate the expedited CMC development of products under an investigational new drug (IND) application, where warranted, based upon the anticipated clinical benefit of earlier patient access to the products. FDA is implementing this pilot program to facilitate CMC readiness for selected Center for Biologics Evaluation and Research (CBER)- and Center for Drug Evaluation and Research (CDER)-regulated products with accelerated clinical development timelines. To accelerate CMC development and facilitate CMC readiness, the pilot features increased communication between FDA and sponsors and explores the use of science- and risk-based regulatory approaches, such as those described in FDA guidance, as applicable. This notice outlines the eligibility criteria and process for submitting a request to participate in the pilot.

CDRP Start Date : April 1, 2023
Duration of CDRP: 2023-2027 (PDUFA VII Period)

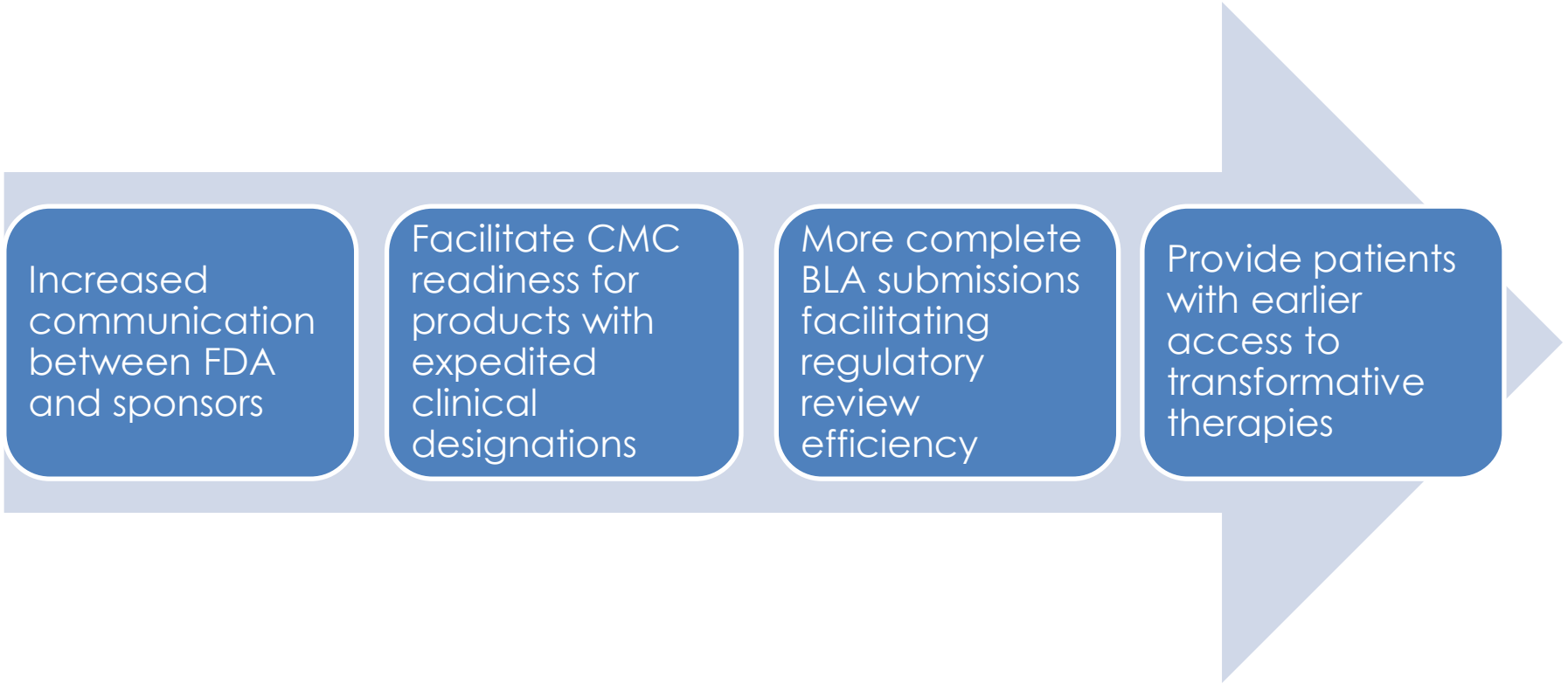
Sponsors of INDs with accelerated clinical development timelines are invited to apply to the CDRP

CDRP aims to:

- Facilitate the expedited CMC development of products
- Increase communication between FDA and sponsors
- Provide patients with earlier access to these products
- A total of 9 INDs will be selected each year (6 CBER and 3 CDER)

Chemistry, Manufacturing, and Controls Development and Readiness Pilot (CDRP) Program | FDA

CDRP Program: Anticipated benefits



Addressing Growth in Cell and Gene Therapy

- The Office of Tissues and Advanced Therapies (OTAT) recently has been reorganized into the Super Office of Therapeutic Products (OTP)
  - Increase interactions with various stakeholders
  - Improve timeliness of responses and meetings
  - Enhance consistency of response

OTP Super Office Structure

Branch | Division | Office | Super Office

Super Office of Therapeutic Products

Super Office Director

Office of Gene Therapy CMC	Office of Cell therapy and Human Tissue CMC	Office of Plasma Proteins Therapeutics CMC	Office of Clinical Evaluation		Office of Pharmacology Toxicology	Office of Review Management and Regulatory Review
Gene Therapy I	**Cell Therapy I**	**Hemostasis**	**General Medicine**	**Oncology**	**Pharm-Tox I**	**DRPM I**
Gene Therapy 1	Cell Therapies 1	Hemostasis 1	General Medicine 1	Oncology 1	Pharm-Tox 1	RPM 1
Gene Therapy 2	Cell Therapies 2	Hemostasis 2	General Medicine 2	Oncology 2	Pharm-Tox 3	RPM 3
Gene Therapy 3	Cellular & Tissue Therapy	**Plasma Derivatives**	General Medicine 3		**Pharm-Tox II**	**DRPM II**
Gene Therapy II	**Cell Therapy II**	Plasma Derivatives 1	General Medicine 4		Pharm-Tox 2	RPM 2
Gene Therapy 4	Tissue Engineering 1	Plasma Derivatives 2	**Hematology**		Pharm-Tox 4	RPM 4
Gene Therapy 5	Tissue Engineering 2		Benign Hematology			
Gene Transfer Immunogenicity	Tumor Vaccine and Biotechnology		Malignant Hematology			
	Human Tissue					
	Human Tissue/ Reproduction					

6 Offices
14 Divisions
33 Branches

DIGITALIZATION OF REGULATORY SUBMISSION

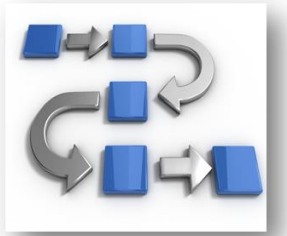
Building Bocks Enabling Digitalization of Regulatory Submission

Paper to E-Submission M4Q(R1)

M4Q(R2)

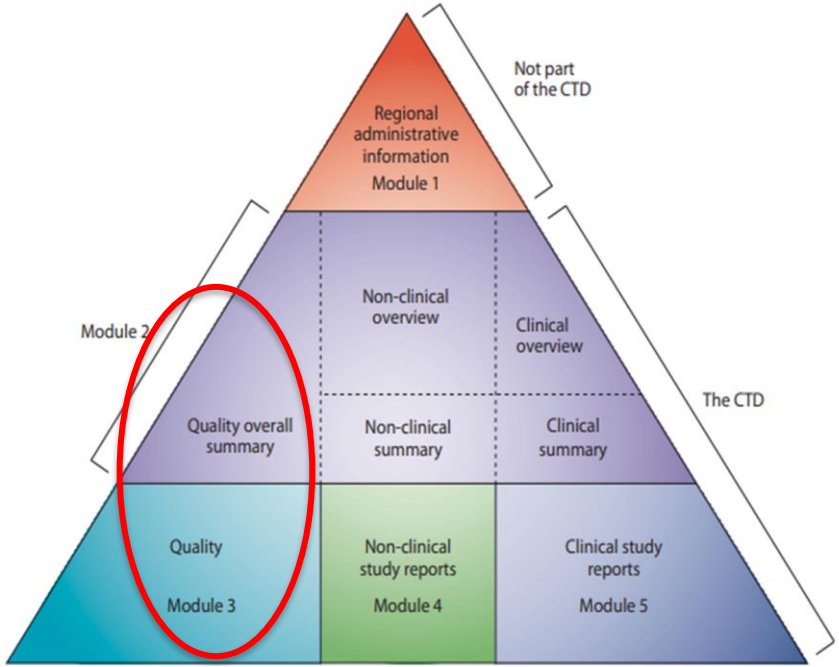
PQ/CMC KASA IDMP/SPOR SPQS

Health Authority Cloud Server



M4Q(R1) ➡ M4Q(R2)

- Provides a harmonized structure and format for presenting quality information in Common Technical Document (CTD)/electronic CTD for registration of pharmaceuticals for human use
  - **Module 2 Quality Overall Summary (QOS**
  - **Module 3 Quality**
- Substantial improvement over wide range of submission formats



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

ICH The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality M4Q(R1) Quality overall Summary of Module 3, Module 3: Quality, September 2002
FDA Guidance for Industry M4Q: The CTD – Quality, August 2001

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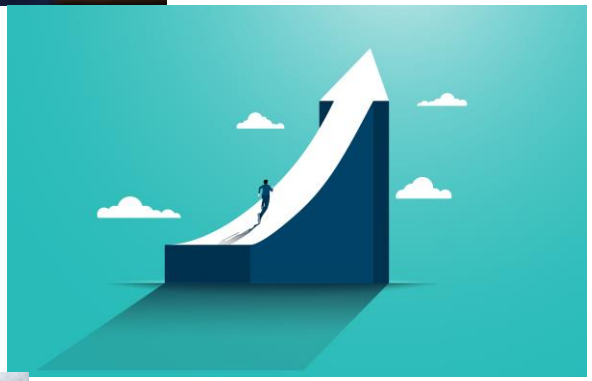
Acknowledgements!

- CBER Leadership:
  - Dr. Peter Marks
  - Dr. Celia Witten
- And the rest of incredibly committed and dedicated CBER staff

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