Harmonization of Field Trials Assessing GM Crops

Duška Stojšin

CLI APEG: Leslie Fuquay, Brad Franklin, James Mickelson, Luciano Jaureguy, Abby Simmons

NAICC Meeting

January 19, 2024

Overview

- Harmonization: Background
- Across Regions
- Across Crops
- Across Developers
- To Harmonize or Not to Harmonize?
- Summary

A Historic Perspective

Harmonization – action or process towards consistency or compatibility

- **Calendar harmonization:**
  - Julian calendar (Roman emperor Julius Caesar) took effect in 46 BC
  - Gregorian calendar (Pope Gregory XIII) first introduced in 1582 (Thursday Oct 4th followed by Friday Oct 15th)
  - Milanković calendar (Serbian scientist Milutin Milanković) proposed in 1923 – more accurate than either Julian or Gregorian, but has not been adopted by any nation as an official calendar
- **Measuring units:**
  - Currently, most countries use International Metric System of Units (except a few including the USA)
- **Right- vs. left-hand traffic:**
  - In most countries, vehicles are driven on the right side of the road, but there are quite a few countries (31%) with left-hand traffic (for example, United Kingdom, India, Australia)
- **Currency:**
  - One country with multiple currencies
  - One country with one currency
  - Multiple countries with the same currency

Harmonization: Field Testing

- Harmonization contributes to simplification, uniformity, convenience, resource saving (cost and time)…
- Requires: planning, agreement, coordination and implementation across multiple teams and stakeholders

Harmonization: Field Testing

- Harmonization of processes associated with field testing of genetically modified (GM) crops are typically initiated by:
  - Regulatory agencies
  - Developers of GM crops
  - Cooperator feedback

Regulatory Agencies

- Need for harmonization recognized by regulatory authorities

From: APHIS Biotechnology Regulatory Services [mailto:APHISBRS@subscribers.usda.gov]
Sent: Friday, March 22, 2013 2:07 PM

APHIS United States Department of Agriculture • Animal and Plant Health Inspection Service
APHIS Stakeholder Registry
protecting the health and value of American agriculture and natural resources

Dear BRS Stakeholder,

The U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) Biotechnology Regulatory Services (BRS) is announcing updated agronomic performance data collection guidance for corn to support a petition for determination of nonregulated status.

Previously, the guidance recommended collecting data from a minimum of 16 sites over one or two years. The new guidance for corn with common agronomic or previously deregulated traits recommends a minimum of eight sites be selected to represent the major growing regions in the U.S targeted for the product. Data from the eight sites may be collected in one or more years. When field-testing corn with less familiar traits or for traits where there is a reason to expect plant pest effects, more sites should be considered. This change is consistent with other international standards and acknowledges the experience gained in over 20 years of corn field tests. The revised guidance can be found at:

http://www.aphis.usda.gov/biotechnology/cornguidance.shtml

efsa
European Food Safety Authority

EFSA Journal 2015;13(6):4128

SCIENTIFIC OPINION

Guidance on the agronomic and phenotypic characterisation of genetically modified plants[1]

EFSA Panel on Genetically Modified Organisms (GMO)[2,3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

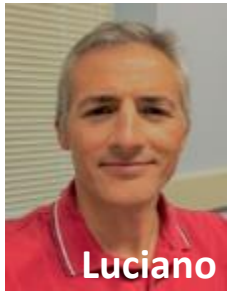
This document provides guidance for the agronomic and phenotypic characterisation of genetically modified (GM) plants and clarifies the EFSA GMO Panel's view on how agronomic and phenotypic data support the risk assessment of GM plants. Specific recommendations are given on (1) the selection of sites and test materials; (2) the quality and design of field trials; (3) the selection of relevant agronomic and phenotypic endpoints; and (4) data analysis. The guidance proposes a comprehensive and harmonised approach for the agronomic and phenotypic characterisation of GM plants, which should ensure the best use of agronomic and phenotypic data for the comparative analysis of GM plants and derived food and feed products, and for their food and feed and environmental risk assessment.

KEY WORDS

comparative analysis, field trials design, invasiveness, persistence, receiving environments, representativeness, unintended effects

Developers of GM Crops

- The Agro-Pheno Expert Group (APEG, previously APET) has been working together since 2015
- 2023 Members:
  - BASF: **Brad Franklin**, Muhammad Bhatti
  - BAYER: **Duška Stojšin**
  - Corteva: **Luciano Jaureguy**, James Mickelson
  - Syngenta: **Leslie Fuquay**
  - CLI: **Abby Simmons**



- Diverse background (genetics, plant biology, statistics, breeding, agronomy, weed science, phytopathology, entomology, GM crops)
- Over 140 years of experience in agriculture

- Industry harmonization and expert guidance regarding agronomic and phenotypic testing (plants, pollen, seed) to support global approval of GM products

Cooperator Feedback

- Field trials are conducted by very specialized cooperators who have experience with sampling and collecting data, regulatory compliance, extensive documentation, and season-long communication, in addition to well-trained staff and well-maintained land and equipment as required to produce high-quality field trials.
- Cooperators tend to conduct field trials for several different developers
- Important for providing feedback

Harmonization Outcomes

- The data and samples collected from your field trials are used to gain GM crop approvals for either import or cultivation in countries/regions like Canada, European Union, UK, China, Korea, Japan…
- Harmonization of processes associated with field testing of GM crops increases uniformity:
  - Across regions
  - Across crops
  - Across developers

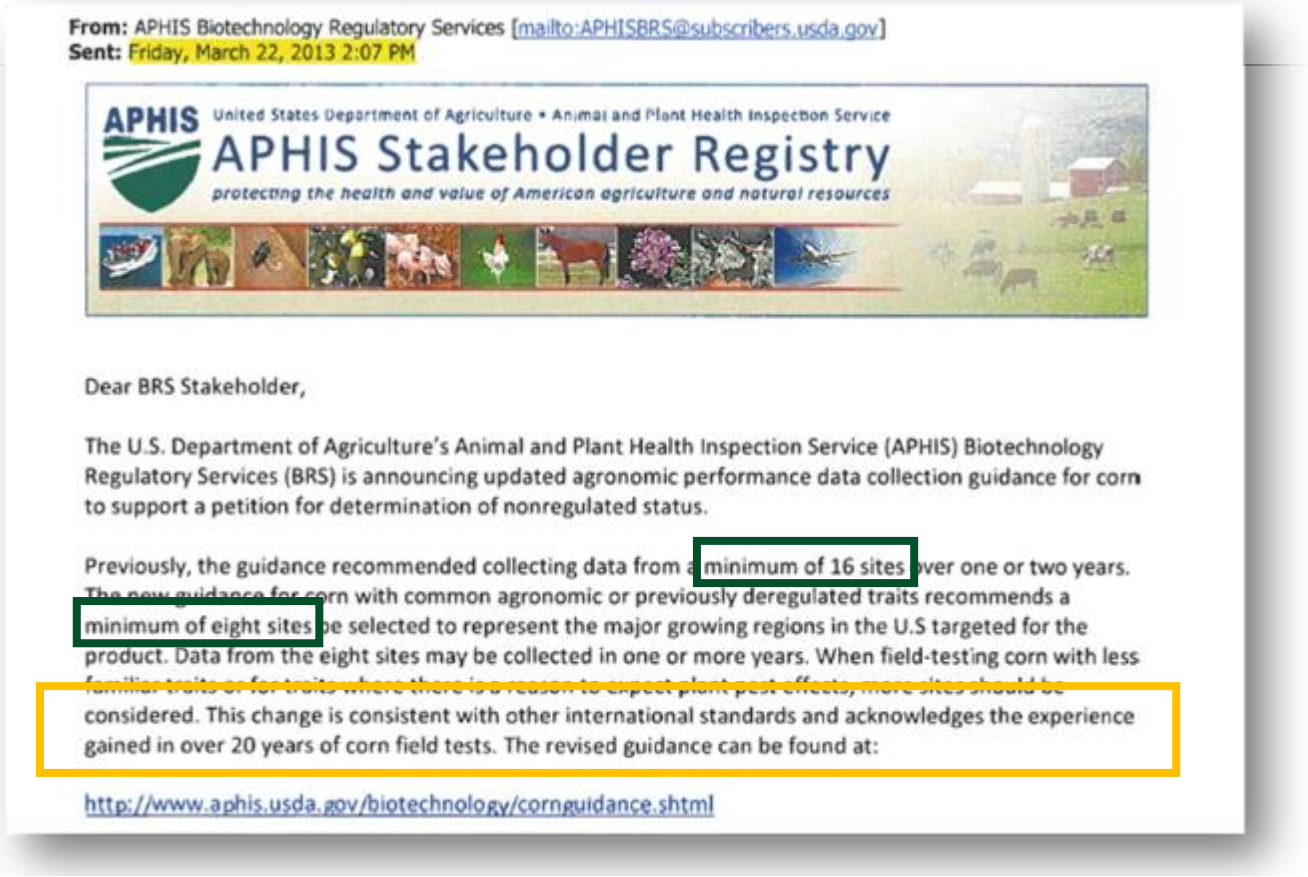
Overview

- Harmonization: Background
- Across Regions
- Across Crops
- Across Developers
- To Harmonize or not to Harmonize
- In Summary

Across Regions: Locations

- **In 2013**, different regulatory agencies had different guidance/requirements regarding number of locations for agronomic and phenotypic field evaluations of GM corn products.

Country (Agency)	Corn
USA (USDA-APHIS)	16
Canada (CFIA)	no guidance
Europe (EFSA)	8
Brazil (CTNBIO)	no guidance
Argentina (CONABIA)	no guidance
Japan (MAFF-MOE)	3
Korea (RDA)	no guidance
China (MOA)	no guidance



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http://www.aphis.usda.gov/biotechnology/cornguidance.shtml

Across Regions: Units

- Agronomic and phenotypic field trials for global submission are conducted mostly in the USA, where Imperial/English unit system is typical.

Submission to USA regulatory agencies

- **Plant characterization**: *e.g.*, plant height (in), grain yield (bu/ac), seedcotton (lb/ac), fiber length (in)…
- **Field details**: *e.g.*, planted area (ac), isolation distance (ft), planting depth (in), plot size (ft x in), precipitation (in), heat stress (˚F)…

Submission to global regulatory agencies

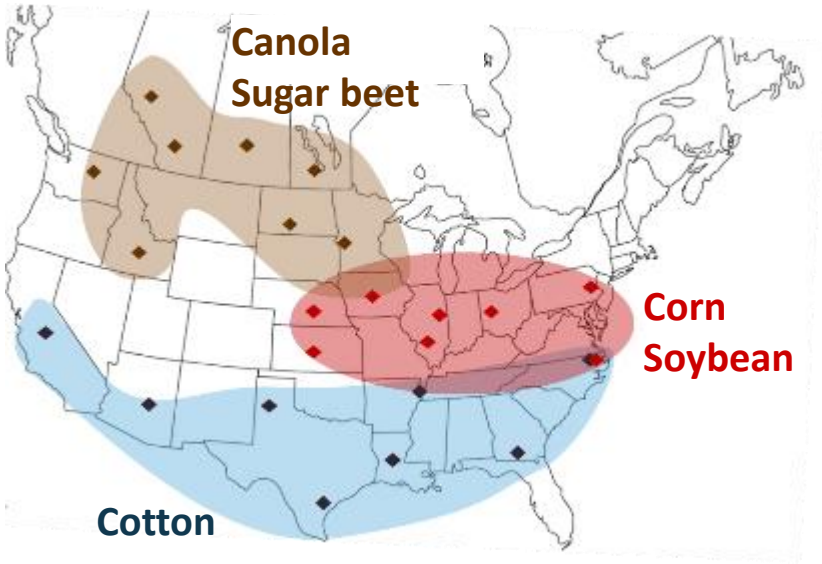
- **Plant characterization**: *e.g.*, plant height (cm), grain yield (t/ha), seedcotton (kg/ha), fiber length (cm)…
- **Field details**: *e.g.*, planted area (ha), isolation distance (m), planting depth (cm), plot size (m x m), precipitation (mm), heat stress (˚C)…

Submission to USA and global regulatory agencies

- **Plant characterization**: *e.g.*, plant height (cm), grain yield (t/ha), seedcotton (kg/ha), fiber length (cm)…
- **Field details**: *e.g.*, planted area (ha), isolation distance (m), planting depth (cm), plot size (m x m), precipitation (mm), heat stress (˚C)…

Across Regions: Endpoints

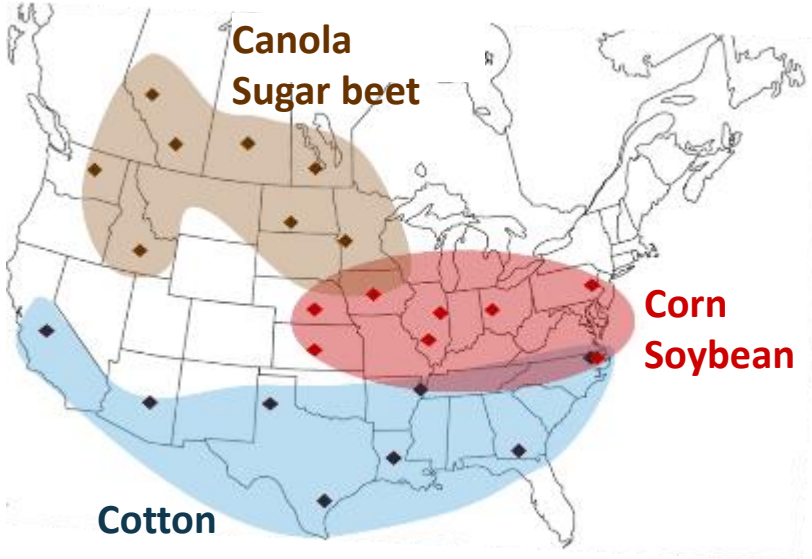
- For studies that have trials conducted in different countries:
  - Field studies to generate agronomic and phenotypic data for regulatory submission may have locations outside of the USA (e.g., Canada, Argentina, Chile)
  - Endpoints (plant characteristics and stressors) to be evaluated need to be harmonized across regions (same endpoints evaluated the same way).
- For products submitted to regulatory agencies in different world regions:
  - If each region requires different data set, then number of evaluated endpoints increases.



Endpoint	Measure [a]	Unit
Early stand count	M	m^2
Days to flowering	V	Days
Lodging [d]	V	No/%
Final stand count	M	m^2
Plant height	M	cm
Days to maturity	V	Days
Fruit count [e]	M	No
Seed moisture	M	%
Seed weight	M	g
Yield	M	g/m^2
Biotic interactions	M/V	–
Abiotic interaction	M/V	–

Across Regions: Units

- Room for harmonization:
  - Canadian cooperators use metric system
  - US cooperators use English unit system
- Would it be practical for the US cooperators to use metric system?
  - Needed for just a few characteristics (plant height, seed weight, and yield)
  - Needed for pesticide concentrations/rates



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Final stand count	M	m^2
Plant height	M	cm
Days to maturity	V	Days
Fruit count [e]	M	No
Seed moisture	M	%
Seed weight	M	g
Yield	M	g/m^2
Biotic interactions	M/V	–
Abiotic interaction	M/V	–

or

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Across Crops: Locations

- **Prior to 2013**, depending on the crop, USDA-APHIS had different guidance on number of locations for agronomic and phenotypic field evaluations of GM crops.

Country (Agency)	Corn	Cotton	Soybean	Canola
USA (USDA-APHIS)	16	12	no guidance	no guidance
Canada (CFIA)	no guidance	no guidance	no guidance	no guidance
Europe (EFSA)	8	8	8	8
Brazil (CTNBIO)	no guidance	no guidance	no guidance	no guidance
Argentina (CONABIA)	no guidance	no guidance	no guidance	no guidance
Japan (MAFF-MOE)	3	3	3	3
Korea (RDA)	no guidance	no guidance	no guidance	no guidance
China (MOA)	no guidance	no guidance	no guidance	no guidance

Across Crops: Stressor Observations

- Field trials in all tested crops include observations of plant responses to crop stressors (abiotic, diseases, and arthropods).
- How to evaluate different stressors uniformly across crops using the same rating scale?






Category	Severity of plant damage
None	No symptoms observed
Slight	Symptoms not damaging to plant development (*e.g.* minor feeding, minor lesions, nutrient deficiency chlorosis); mitigation likely not required
Moderate	Intermediate between slight and severe; likely requires mitigation
Severe	Symptoms damaging to plant development (*e.g.* stunting or death); mitigation unlikely to be effective

Across Crops: V/R vs BBCH

- Different plant developmental scales are used depending on the crop:
  - V/R scale for corn and soybean
  - BBCH scale for canola and cotton
- Requirement from a regulator drove towards harmonization – reporting BBCH stages across crops

Endpoint	Measure [a]	Unit	Growth stage [b] (BBCH)			
			Soybean	Maize	Cotton	Oilseed rape
Early stand count	M	m^2	12–13	11–14	11–13	11–13
Days to flowering	V	Days	61–69	61–69	61–69	61–69
Lodging [d]	V	No/%	89	89	89	80–89
Final stand count	M	m^2	89	87–89	89	31–99
Plant height	M	cm	89	69–89	69–89	71–89
Days to maturity	V	Days	89	87	89	89
Fruit count [e]	M	No	89	89	89	89
Seed moisture	M	%	99	99	99	99
Seed weight	M	g	99	99	99	99
Yield	M	g/m^2	99	99	99	99
Biotic interactions	M/V	–	11–99	11–99	11–99	11–99
Abiotic interaction	M/V	–	11–99	11–99	11–99	11–99

//www.corteva.co.uk/

Across Crops:

- Different endpoints were evaluated across crops
- Requirement from a regulator drove towards harmonization – standardize endpoints across crops

Endpoint	Measure [a]	Unit	Growth stage [b]			
			Soybean	Maize	Cotton	Oilseed rape
Early stand count	M	m^2	12–13	11–14	11–13	11–13
Days to flowering	V	Days	61–69	61–69	61–69	61–69
Lodging [d]	V	No/%	89	89	89	80–89
Final stand count	M	m^2	89	87–89	89	31–99
Plant height	M	cm	89	69–89	69–89	71–89
Days to maturity	V	Days	89	87	89	89
Fruit count [e]	M	No	89	89	89	89
Seed moisture	M	%	99	99	99	99
Seed weight	M	g	99	99	99	99
Yield	M	g/m^2	99	99	99	99
Biotic interactions	M/V	–	11–99	11–99	11–99	11–99
Abiotic interaction	M/V	–	11–99	11–99	11–99	11–99

Endpoints	Corn	Soybean	Cotton	Canola
Vigor				
Early plant height				
Early stand count				
Stand count at 30 DAP				
Days to flowering				
Days to 50% silking				
Stay green				
Flower color				
Nodes above white flower				
Main stem nodes				
Immature seed/boll				
Ear height				
Plant height				
Seed maturity				
Fruit/seed loss				
Plant lodging				
Root lodging				
1st position bolls				
Fruit count				
Final stand count				
1st position fruit retention				
Days to maturity				
Seed moisture				
Seed weight				
Seed index				
Seed per ball				
Seed quality				
Yield				
Fiber micronaire				
Fiber elongation				
Fiber strength				
Fiber length				
Fiber uniformity				
Response to abiotic stress				
Disease damage				
Arthropod damage				

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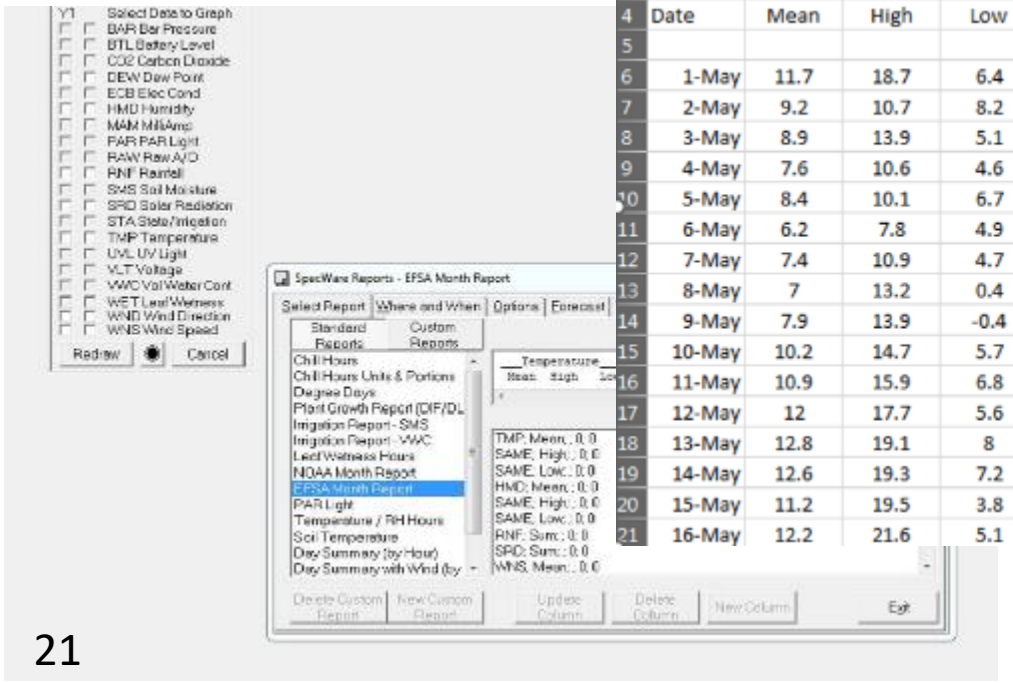
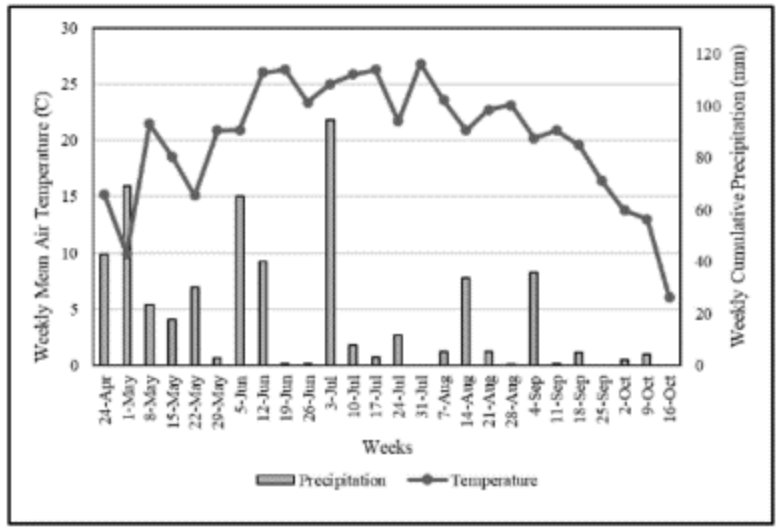
Across Developers: Weather Data

- A few years ago, during NAICC meeting, a feedback from several cooperators was the lack of consistency in weather data collection across developers
- Three-party initiative (cooperator, developer, and weather station provider) resulted in more harmonized weather station output
- Customized weather data forms were developed to better meet regulator requirements with standardized units, data collection interval, reporting format



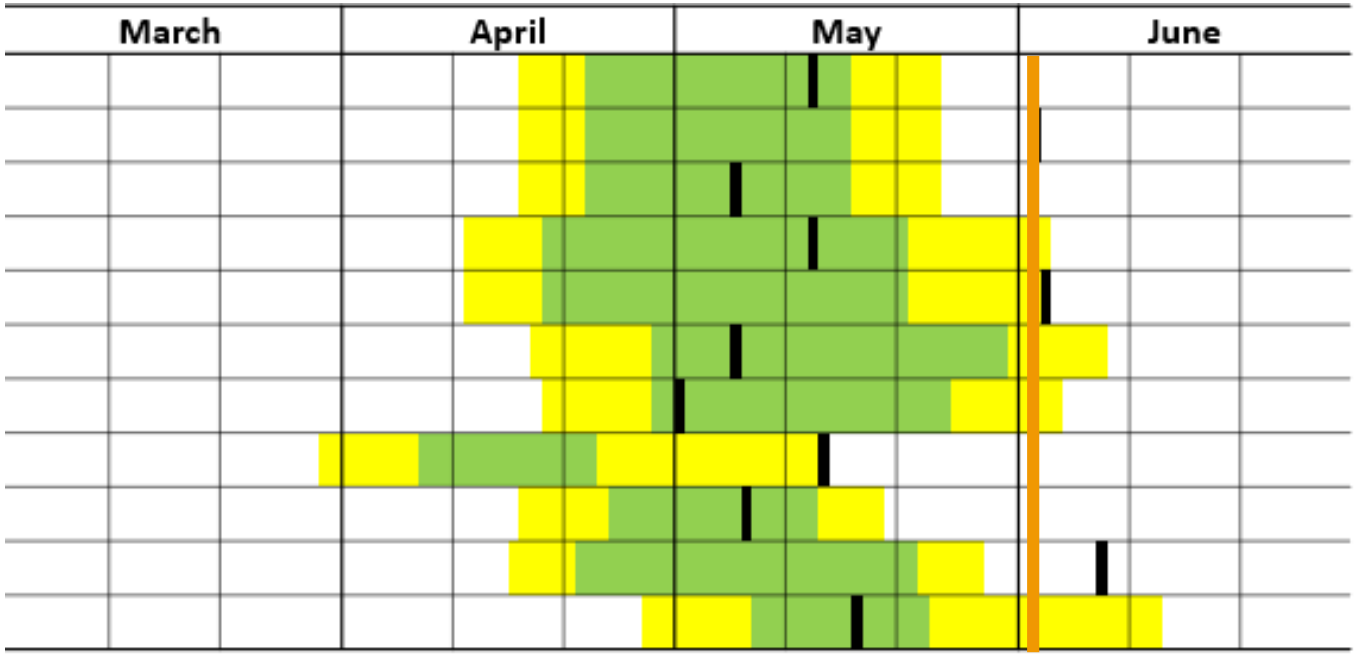
	Temperature °C			RH %			Rainfall	Global Radiation	Wind m/s		
Date	Mean	High	Low	Mn	High	Low	mm	MJ/m2	Mean	Gust	Low
1-May	11.7	18.7	6.4	99	100	92	34.3	4.1	1.1	6.9	0
2-May	9.2	10.7	8.2	88	97	80	1.6	8.8	3.6	12.8	1.1
3-May	8.9	13.9	5.1	73	95	44	0	23.2	1.6		
4-May	7.6	10.6	4.6	91	100	60	13.3	4.8	0.7		
5-May	8.4	10.1	6.7	100	100	100	40.1	3.8	2.2		
6-May	6.2	7.8	4.9	99	100	95	2.8	5.3	2.2		
7-May	7.4	10.9	4.7	73	100	54	1.2	15.8	1.9		
8-May	7	13.2	0.4	57	90	34	0	25.2	1.3		
9-May	7.9	13.9	-0.4	56	87	34	0	23.4	0.6		
10-May	10.2	14.7	5.7	56	79	39	0	23.5	1.2		
11-May	10.9	15.9	6.8	57	71	42	0	13	1.5		
12-May	12	17.7	5.6	70	95	46	0	13	0.6		
13-May	12.8	19.1	8	77	98	50	0.5	17.5	0.8		
14-May	12.6	19.3	7.2	71	100	33	0.2	21	1.6		
15-May	11.2	19.5	3.8	73	100	42	0	25.2	1.2		
16-May	12.2	21.6	5.1	83	100	47	0.2	12.4	0.5		



Across Developers: Planting Time

- Based on cooperator feedback during NAICC, the developers were able to harmonize approach to planting field trials
- Different approaches due to differential interpretation of regulator's request

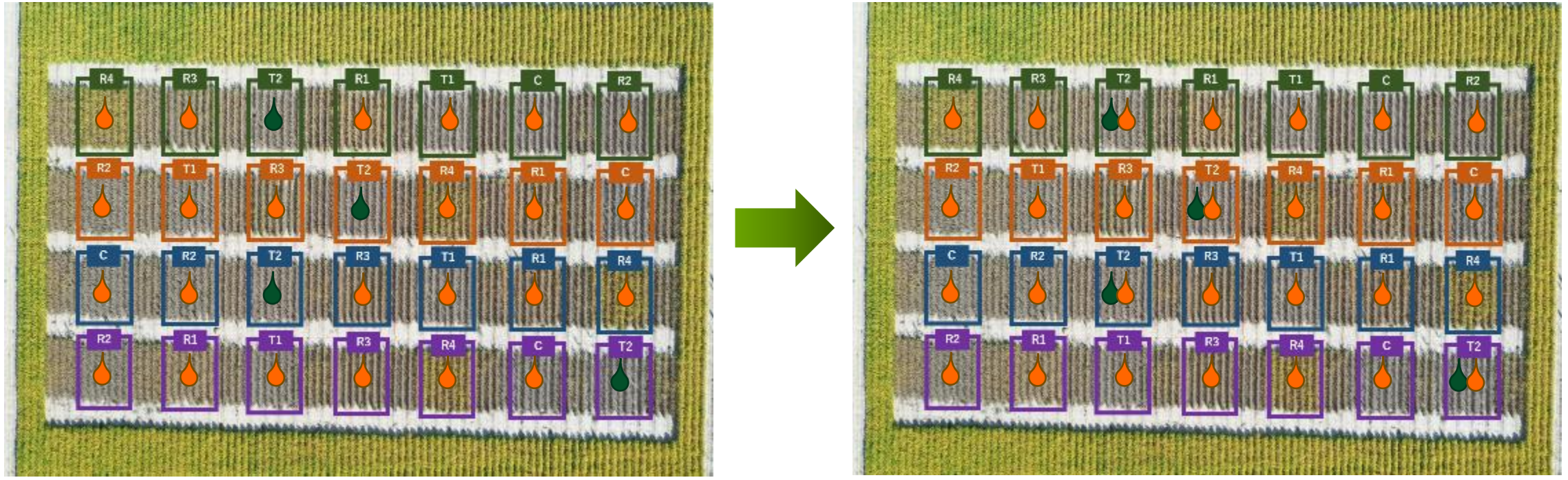
1. Soil sampling 2. Planting 3. Soil results	or	1. Soil sampling 2. Soil results 3. Planting	→ 1. Soil sampling 2. Planting 3. Soil results



- Less risk due to earlier planting window
- More flexibility for planting

Across Developers: Herbicide Used

- Based on cooperator feedback, the developers were able to harmonize approach to application of maintenance herbicides.
- Previously, some applied maintenance herbicide uniformly across all entries, others have not (in order to adjust for intended herbicide applied on test entries) due to different interpretation of regulator guidance.
- As of 2023 season, CLI APEG members have been using maintenance herbicides uniformly across entries.



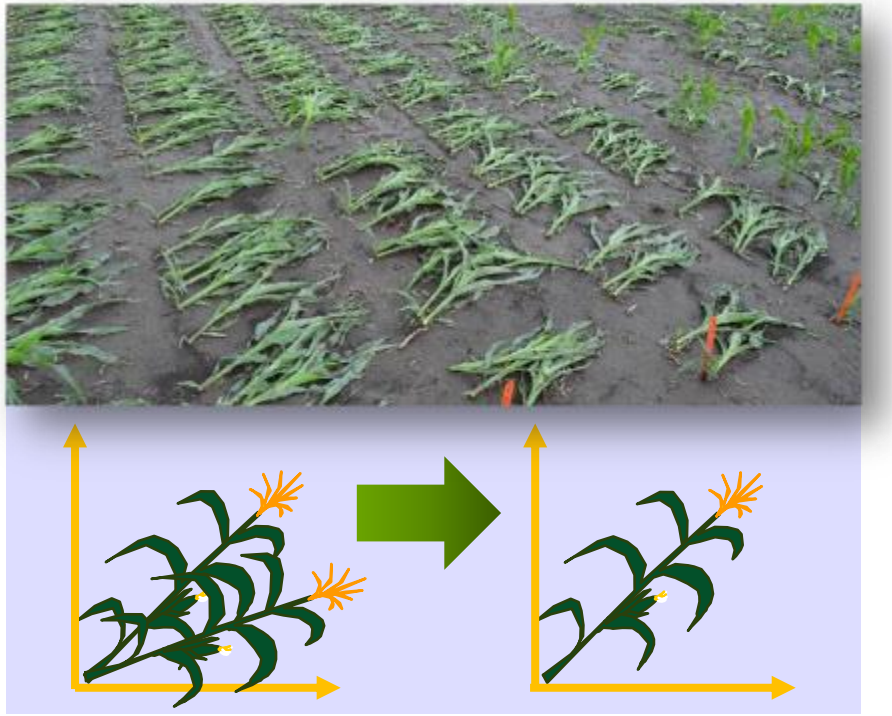
Across Developers: Endpoints

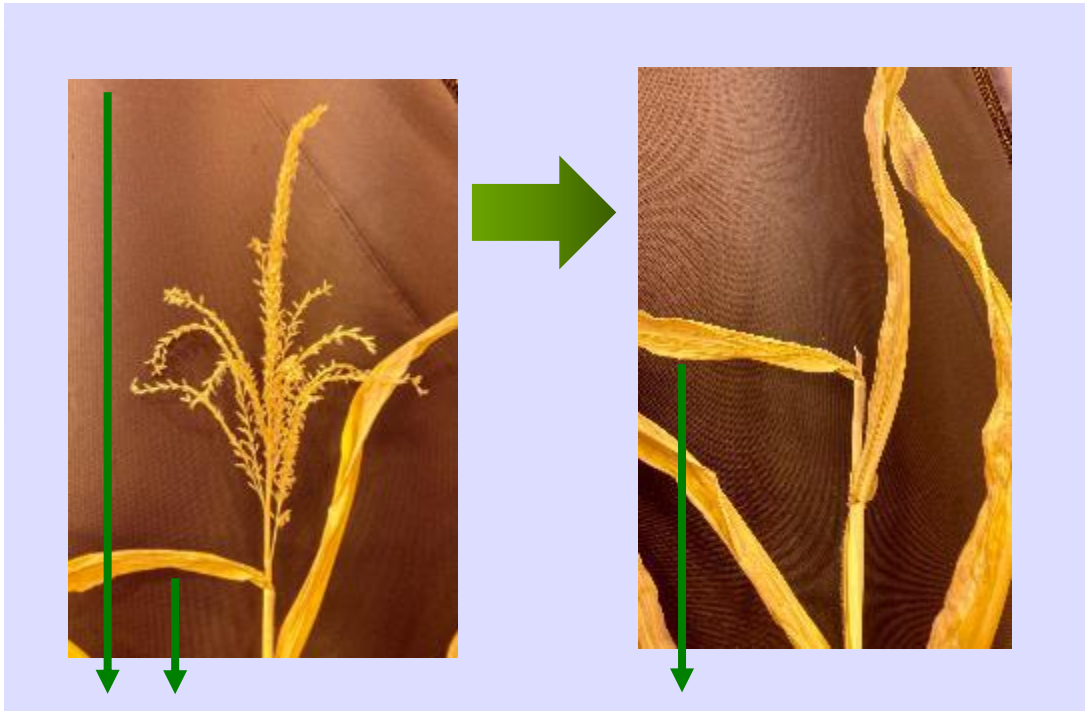
Corn	Developer 1	Developer 2	Developer 3	Developer 4	Developer 5
Emergence					
Early growth rating					
Vigor					
Early stand count					
Green snapped plants					
Herbicide injury					
Days to 50% pollen shed					
Days to 50% silking					
Stay green					
Leaf color					
Ear diameter					
Ear height					
Plant height					
Dropped ear count					
Plant lodging					
Late season intactness					
Fruit count					
Final stand count					
Days to maturity					
Barren plants					
Grain moisture					
Test weight					
Seed weight					
Yield					
Response to abiotic stress					
Disease damage					
Arthropod damage					

- Prior to 2017, every developer of GM products had different plant characterization strategy.
- Among 5 developers, a total of 28 corn endpoints were assessed, but only 6 were in common
- Number of evaluated corn endpoints ranged from 8 to 19.
- After 2017, CLI-APEG harmonization effort resulted in fewer than 15 endpoints across developers

Across Developers: Data Collection

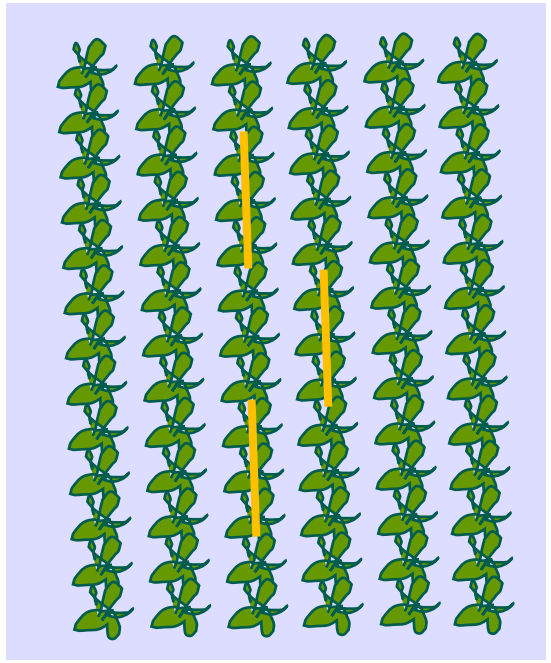
- Within Crop Life International, developers have been working towards harmonizing details regarding data collection:
  - Lodged plants were defined as those that are leaning either 30 or 45 degrees. Currently, we all define lodged plants as those leaning more than 45 degrees.
  - Corn plant height was evaluated either to the top of the tassel or to the flag leaf. Currently, we all define corn plant height as a distance from the soil level to the flag leaf.

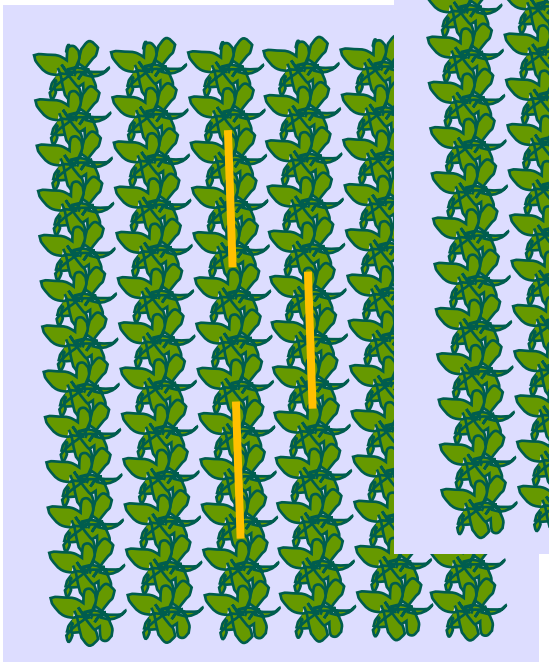


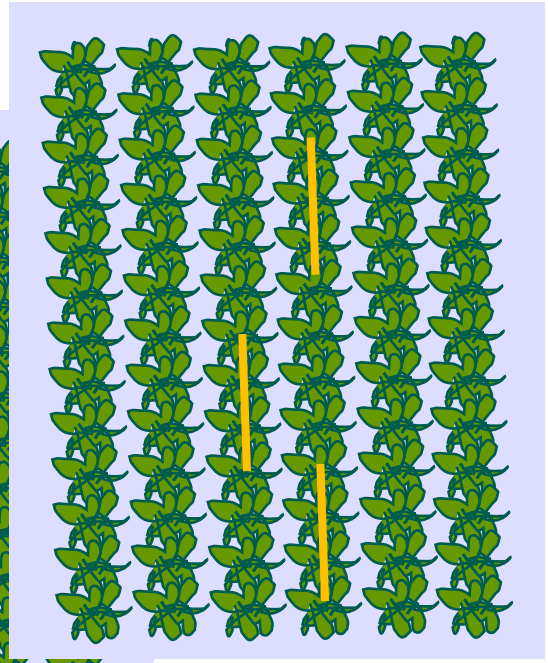


Across Developers: Data Collection

- Room for harmonization includes details regarding data collection:
  - Number of plants needed for plant height assessment varies across developers. Some request evaluation of 5, others 10 plants per plot.
  - For early and final stand count of soybean, some consider counting all the plants in evaluation rows, others focus on three 1-meter row sections (which can be the same or different for the two characteristics).
  - Other considerations?







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A Historic Perspective

For objective or subjective reasons, harmonization might not always work.

Language:

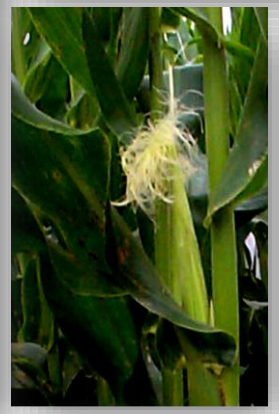
- Estimated 5,000 to 7,000 languages worldwide
- A need to communicate across language groups resulted in some level of harmonization:
  - Historically, Greek and Latin were used as a language of scholars
  - By 17th century, French was known as the language of diplomacy and international relations throughout the world
  - In 1887, Esperanto was invented as an international language
  - Currently, English is recognized as a global language
- However, it is hard to imagine full harmonization (one language as a mother tongue for all)

To Harmonize or Not to Harmonize

- Similarly, full harmonization GM field trials is not necessarily feasible
- Uniformity is not always practical, nor scientifically justified

- For example, cross- vs self-pollinated crops; yield of grain, lint, roots…






To Harmonize or Not to Harmonize

- For cotton, seed moisture cannot be measured at harvest, but after processing
- Canola needs to be cut/pushed prior to reaching maturity to avoid seed loss
- Sugarbeet roots are harvested prior to flowering or seed setting

- There are limits to harmonization due to differences in crop biology or agronomic practices

Endpoint	Measure [a]	Unit	Growth stage [b]			
			Soybean	Maize	Cotton	Oilseed rape
Early stand count	M	m^2	12–13	11–14	11–13	11–13
Days to flowering	V	Days	61–69	61–69	61–69	61–69
Lodging [d]	V	No/%	89	89	89	80–89
Final stand count	M	m^2	89	87–89	89	31–99
Plant height	M	cm	89	69–89	69–89	71–89
Days to maturity	V	Days	89	87	89	89
Fruit count [e]	M	No	89	89	89	89
Seed moisture	M	%	99	99	99	99
Seed weight	M	g	99	99	99	99
Yield	M	g/m^2	99	99	99	99
Biotic interactions	M/V	–	11–99	11–99	11–99	11–99
Abiotic interaction	M/V	–	11–99	11–99	11–99	11–99

To Harmonize or Not to Harmonize

- In 2019, EFSA mandated analyzing pollen tissue for GM protein expression.
- Large amounts of pollen cannot be collected from some crops due to the biological limits.
- In 2021/2022, EFSA adjusted the requirement to account for crop-to-crop specificity.

Crop	Flowers needed per entry, per site
Corn	24
Cotton	280
Canola	14.100
Soybean	400.000

Summary

- Harmonization is an action or process towards consistency or compatibility
- A key contributor to advancements of society and science throughout history
  - Has resulted in simplification, uniformity, convenience, resource savings (cost and time)
  - Initially might take more time and effort
- Continuous process

- Harmonization associated with field trials conducted for plant characterization of GM crops can be:
  - Initiated by regulators, GM developers, or cooperators
  - Done across regions, crops, and developers

- In some cases, full harmonization is not feasible, practical, of scientifically justified:
  - Differences among GM products
  - Different crop biology

- Discussion goals:
  - Share some examples of harmonization effort associated with GM field trial testing
  - Thank you for your feedback and encourage future suggestions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