Biosimilar Substitution

A Collaborative Approach to Pharmacovigilance

Philip J. Schneider, M.S., F.A.S.H.P.
Advisory Board Chair, Alliance for Safe Biologic Medicines

September 30, 2018

Background

- **Responsible use of biologic and biosimilar medicines is complicated**
  - Efficacy/effectiveness gap
  - Safety/preventable adverse drug events
  - Innovation/affordability conflicts
- **Medication-use is a team effort**
  - The greatest value from an investment in pharmacotherapy results from collaboration among health care professionals and patients
- **Accountability**
  - Health care professionals -> their patient (Regulated by the States)
  - Pharma -> innovations for patients (Regulated by the Federal Gov't)
  - Insurance companies/PBMs -> Saving money (Regulated???)

Benefits of Biosimilar Medicines

Increased treatment choices:

- Patients with conditions treated by biologics often struggle for years, trying multiple products, before becoming stable.

Cost savings:

- Unlike generics, which save 40-80%, due to higher development costs biosimilars are expected to save payers 15-30%.[1]
- A 2014 RAND Corporation study estimated 10-35% cost reduction in U.S. [2]
- In Europe, savings of between 25%-70% have been seen. [3]

1 Generics and Biosimilars Initiative Journal (GaBI Journal). 2012;1(3-4).120-6. DOI: 10.5639/gabij.2012.0103-4.036
2 https://www.rand.org/content/dam/rand/pubs/perspectives/PE100/PE127/RAND_PE127.pdf
3 http://www.fiercepharma.com/story/merck-discounts-remicade-uk-it-tries-fend-biosimilars/2015-10-26

Issues Surrounding Biosimilar Substitution

- Under what circumstances may a pharmacist substitute a biosimilar (approved by FDA as interchangeable) without the involvement of the physician
- What communication is required between pharmacist and:
  - Physician
  - Patient
- What records must be kept of the substitution?
- This is the purview of state government: Legislatures, Boards of Pharmacy

Why are these Concerns Important?

- Patient always needs to be informed about the medicine he/she is receiving in order to make informed choices and be an effective partner in care.
- Physician needs to be aware of what medicine patient is receiving to provide proper care.
- Accurate patient record must be kept for pharmacovigilance/post-market monitoring for adverse events and efficacy
- Physicians and pharmacists have a responsibility to the patient and to the larger community (other healthcare providers, regulators, manufacturers) to work collaboratively together – that includes **clear, timely communication.**

EU and Canada: Oppose Automatic Substitution But Leave to Provinces/Member States

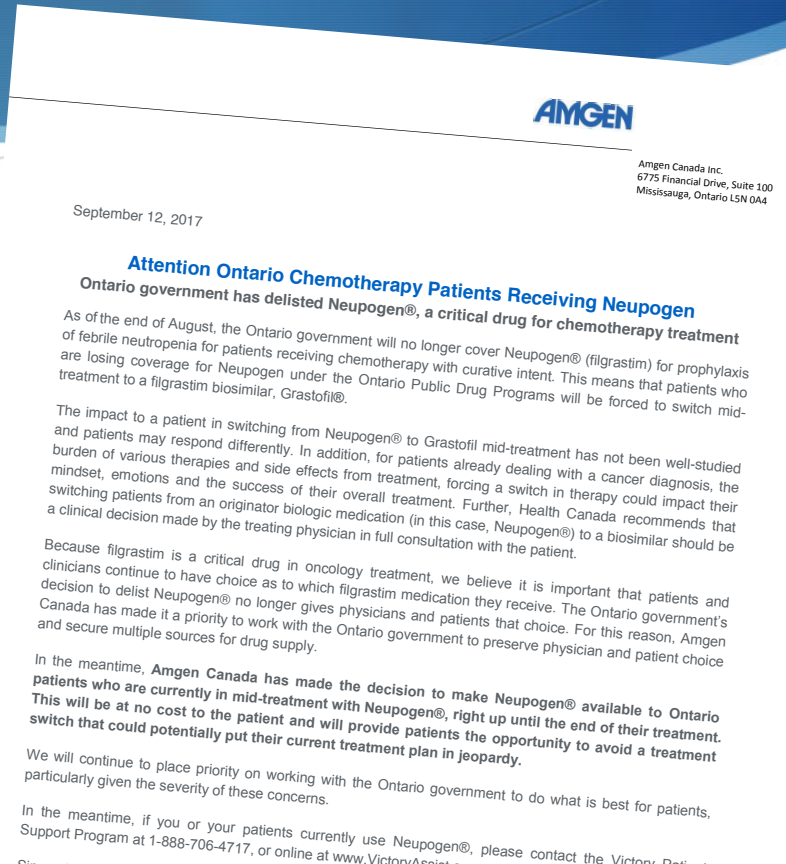
- The EMA advises that: "the physician should be in charge of the decision to switch between the reference and biosimilar, or vice versa."[1]
- "Health Canada does not support automatic substitution of a Subsequent Entry Biologic for its reference biologic drug and recommends that physicians make only well informed decisions regarding therapeutic interchange".[2]

1 European Medicines Agency. Questions and Answers on Biosimilar Medicines (Similar Biological Medicinal Products). London: European Medicines Agency; 2012. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf. Accessed November 6, 2012.

2 http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/seb-pbu/01-2010-seb-pbu-qa-qr-eng.php

Ontario Delisting of Neupogen (filgrastim) 2017

"As of the end of August, the Ontario government will **no longer cover Neupogen® (filgrastim)** for prophylaxis of febrile neutropenia for patients receiving chemotherapy with curative intent. This means that patients who are losing coverage for Neupogen under the Ontario Public Drug Programs will be **forced to switch mid-treatment** to a filgrastim biosimilar, Grastofil®."



AMGEN

Amgen Canada Inc.
6775 Financial Drive, Suite 100
Mississauga, Ontario L5N 0A4

September 12, 2017

Attention Ontario Chemotherapy Patients Receiving Neupogen

Ontario government has delisted Neupogen®, a critical drug for chemotherapy treatment

As of the end of August, the Ontario government will no longer cover Neupogen® (filgrastim) for prophylaxis of febrile neutropenia for patients receiving chemotherapy with curative intent. This means that patients who are losing coverage for Neupogen under the Ontario Public Drug Programs will be forced to switch mid-treatment to a filgrastim biosimilar, Grastofil®.

The impact to a patient in switching from Neupogen® to Grastofil mid-treatment has not been well-studied and patients may respond differently. In addition, for patients already dealing with a cancer diagnosis, the burden of various therapies and side effects from treatment, forcing a switch in therapy could impact their mindset, emotions and the success of their overall treatment. Further, Health Canada recommends that switching patients from an originator biologic medication (in this case, Neupogen®) to a biosimilar should be a clinical decision made by the treating physician in full consultation with the patient.

Because filgrastim is a critical drug in oncology treatment, we believe it is important that patients and clinicians continue to have choice as to which filgrastim medication they receive. The Ontario government's decision to delist Neupogen® no longer gives physicians and patients that choice. For this reason, Amgen Canada has made it a priority to work with the Ontario government to preserve physician and patient choice and secure multiple sources for drug supply.

In the meantime, **Amgen Canada has made the decision to make Neupogen® available to Ontario patients who are currently in mid-treatment with Neupogen®, right up until the end of their treatment. This will be at no cost to the patient and will provide patients the opportunity to avoid a treatment switch that could potentially put their current treatment plan in jeopardy.**

We will continue to place priority on working with the Ontario government to do what is best for patients, particularly given the severity of these concerns.

In the meantime, if you or your patients currently use Neupogen®, please contact the Victory Patient Support Program at 1-888-706-4717, or online at www.VictoryAssist.

Automatic Substitution Policy Around the World

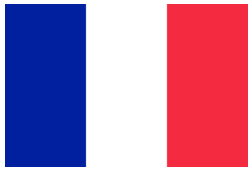
AUSTRALIA: Permits automatic substitution (“a-flagging”) of biosimilars, physicians can prevent substitution.

LATIN AMERICA: A range of policies. Where protections exist for physician prescriptive autonomy, enforcement is not consistent.

EUROPE: EMA opposes, left to member states. BANNED BY MOST STATES except for Estonia, France, Latvia, Poland and Russia. Prescriptions are generally done by INN alone.

Automatic Substitution Policy Around the World

ESTONIA: Patient can refuse and pay price difference out of pocket.



FRANCE: substitution permitted for bio-naïve patients, pharmacist-physician communication required, physician can prevent. (not yet implemented)

LATVIA: Non-bio-naïve patients can refuse and pay cost difference, physician can prevent. Others must use cheapest product.

POLAND: allowed by law, pharmacists are to discuss with patient.

Automatic Substitution Policy Around the World

GERMANY: Unless prevented by physician, pharmacists may substitute “BIOIDENTICALS” ONLY (Biosimilars to the same reference product that are made by the same manufacturer but marketed under different trade names, e.g. Inflectra and Remsima infliximab).

RUSSIA: Physicians prescribe by INN, but can prevent substitution for a medical reason. Patients can buy brand name out of pocket.

Biosimilar Substitution Policy in the U.S.

- US: 45 states permit substitution of “interchangeable” biosimilars.
- In these states, physicians can prevent substitution and are to be communicated which product was dispensed.
- FDA silent on pharmacy substitution of non-interchangeable biosimilars.
- Private payers are beginning to exclude originator products from formulary.

Recap: Interchangeability

A US-Specific higher regulatory standard to meet. More data is required.

An "INTERCHANGEABLE" Biosimilar :

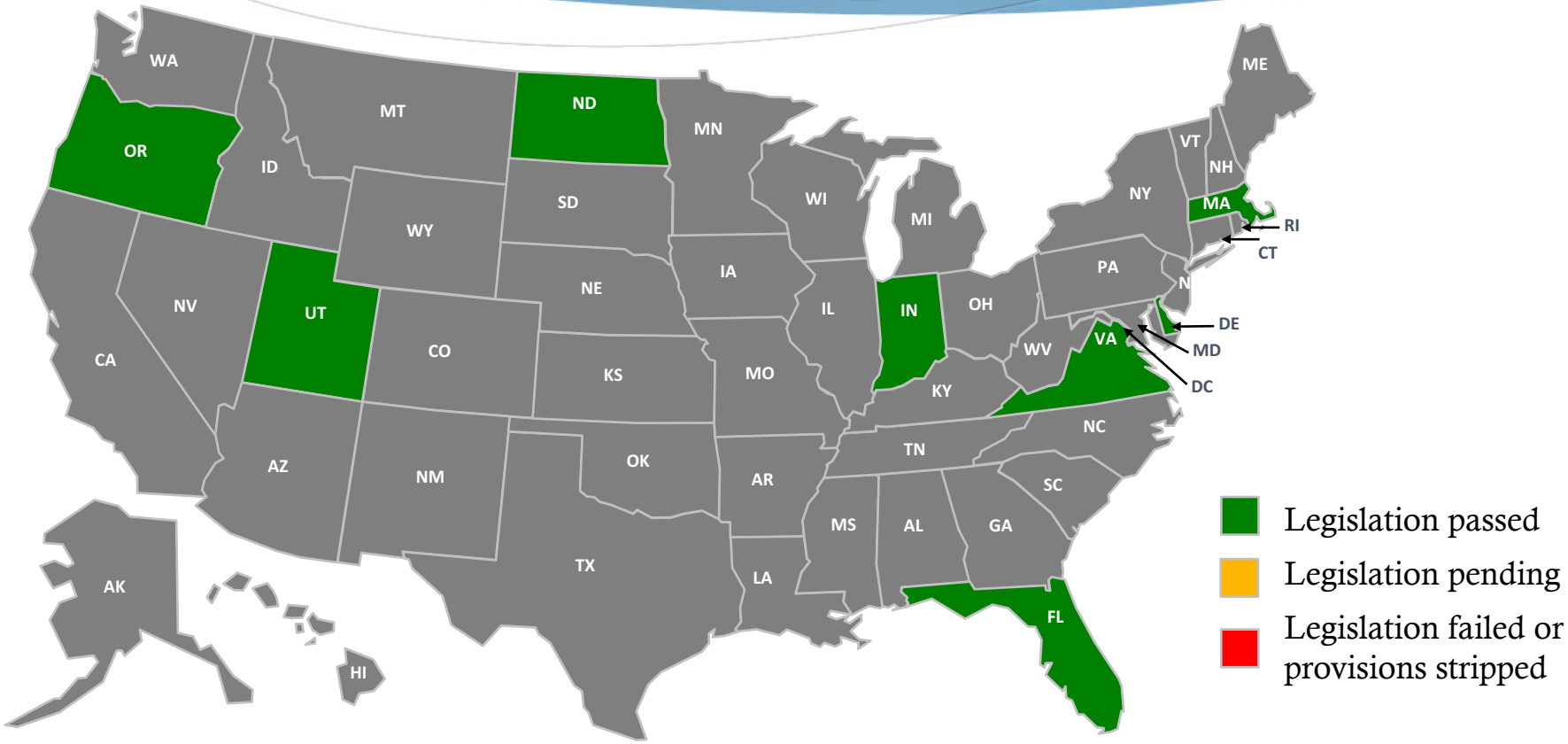
1) Must be **biosimilar** ("highly similar" to reference product).
2) Must have **same clinical result** expected as with reference product.
3) Must create **no additional risk to patient** when switching back and forth between itself and reference product.
4) **May be substituted for the reference product without the intervention of the prescriber.**

Nevertheless, 45 states and Puerto Rico have laws requiring pharmacist-physician communication when biosimilar substitution is a possibility.

Common Features of U.S. State Substitution Laws

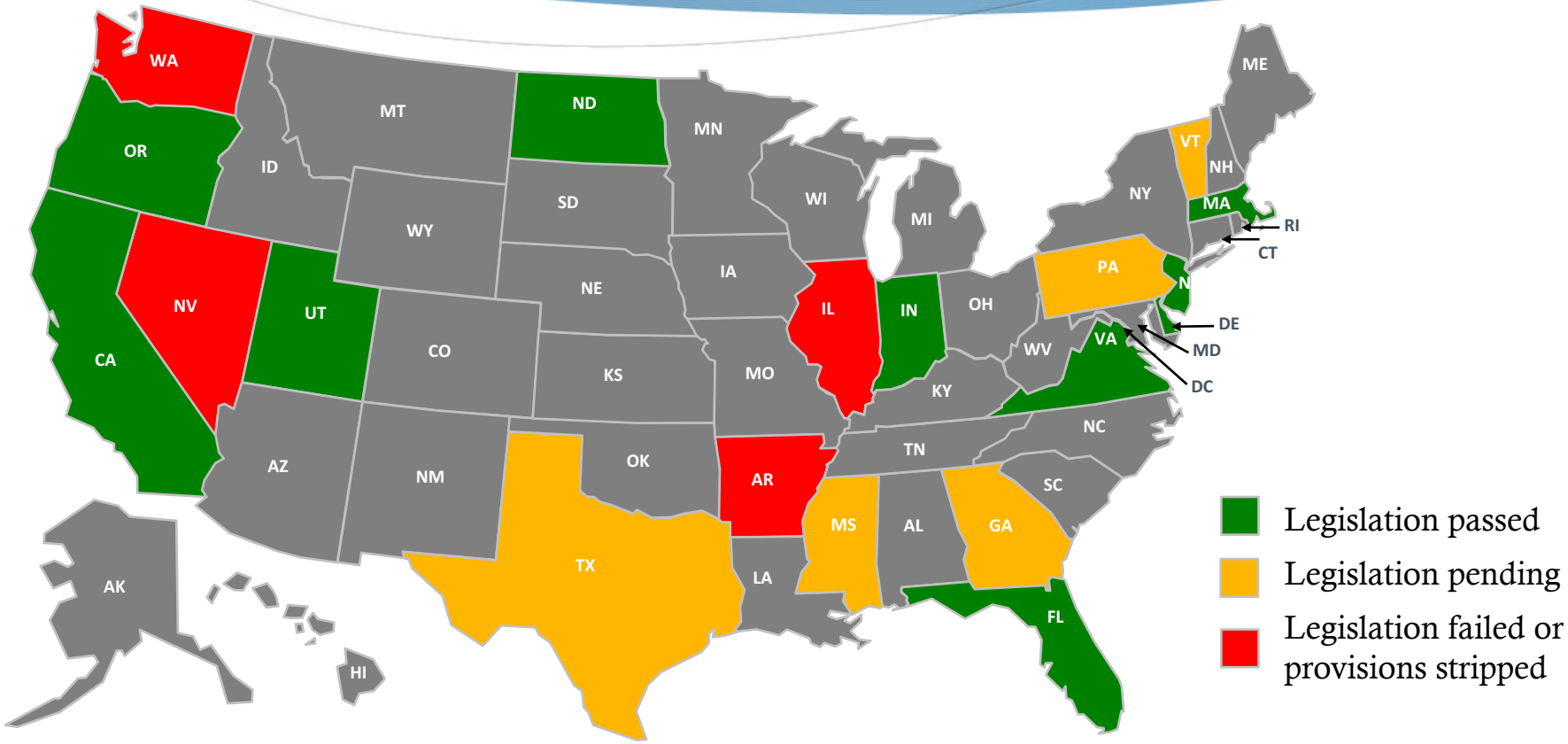
- Permits only substitution of "interchangeable" biosimilars.
- Require pharmacist to communicate which product – biosimilar or reference- was dispensed to patient within 3-5 business days.
- Allow physician to specify "do not substitute" or similar.
- Pharmacist to keep records for 2 years.

2014: Communication Requirements by State



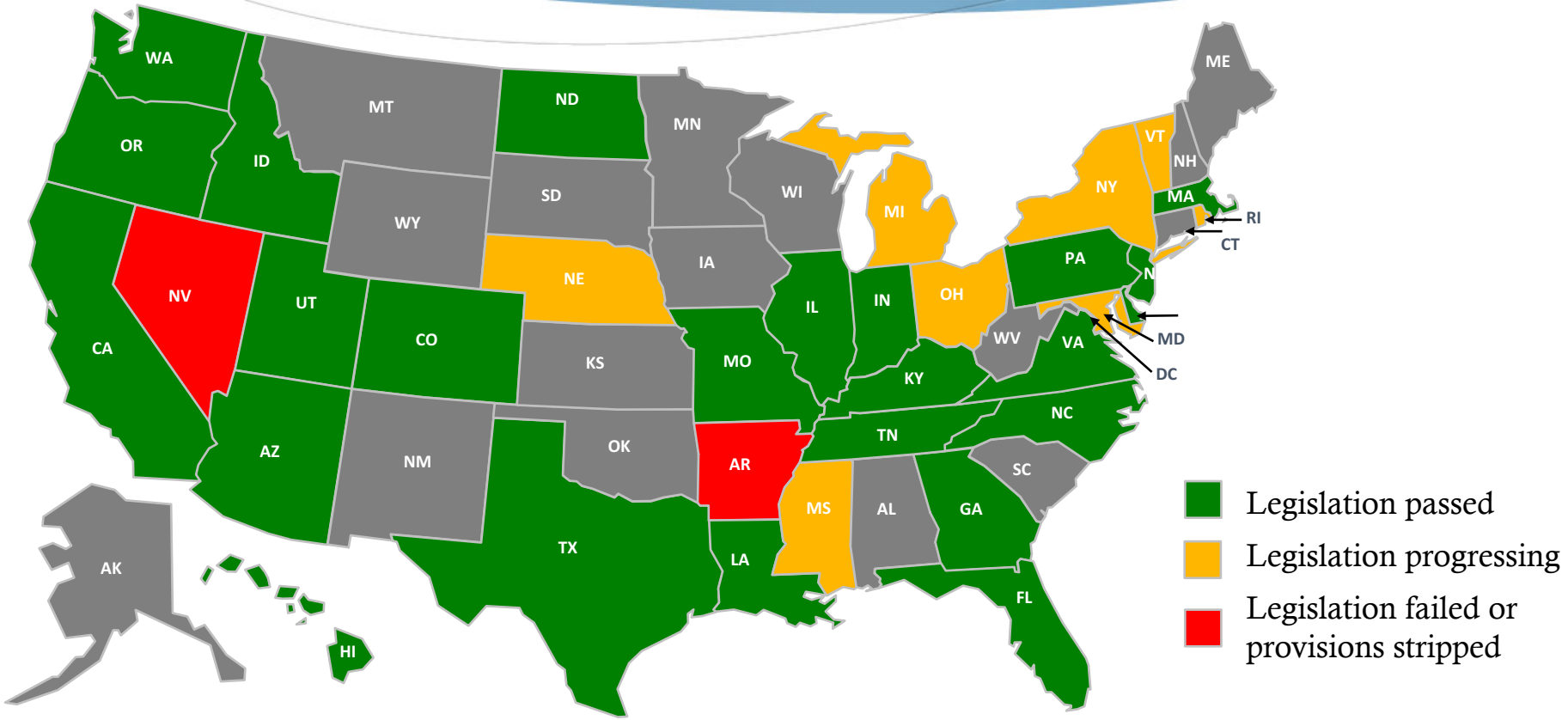
Rev. 11/15

2015: Communication Requirements by State



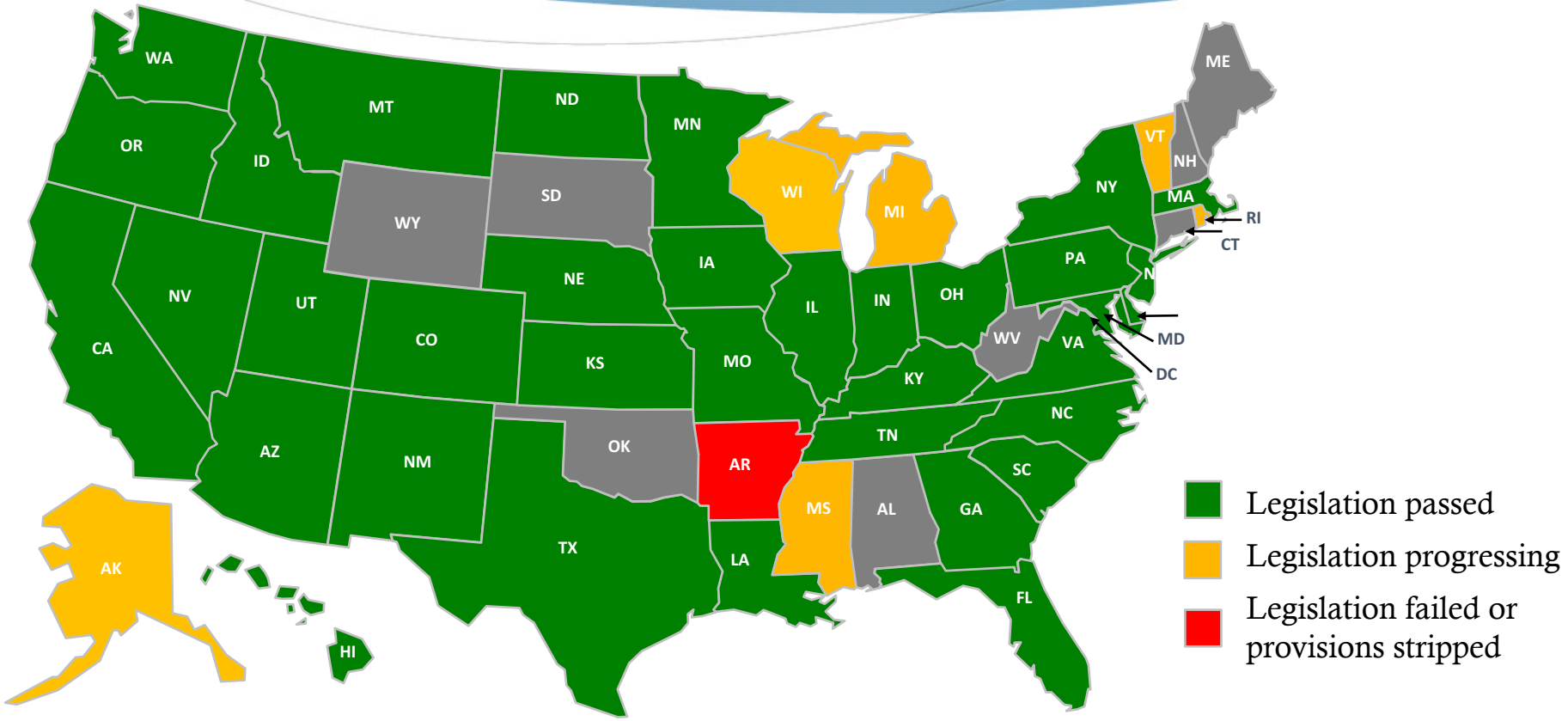
Rev. 11/15

2016: Communication Requirements by State



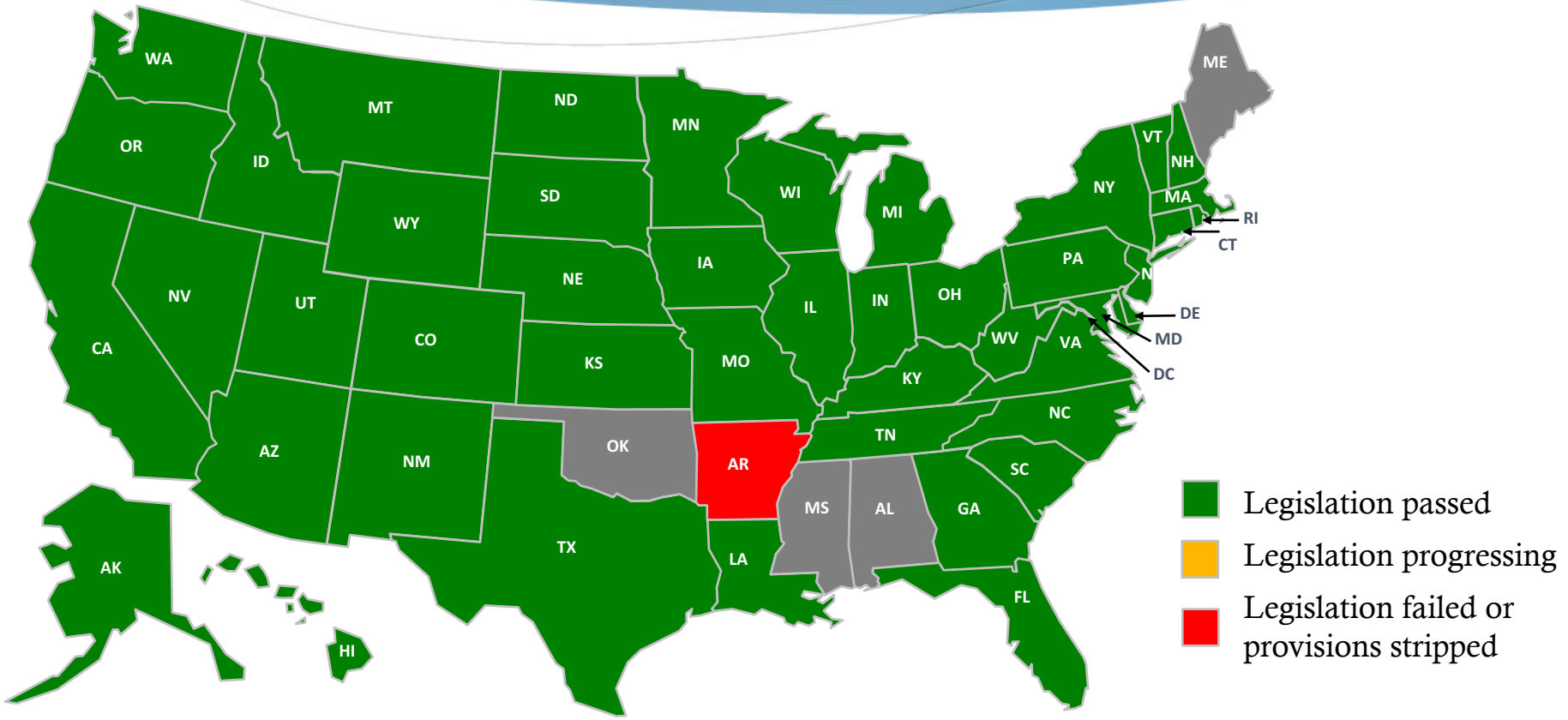
Rev. 09/14/16

2017: Communication Requirements by State



Rev. 12/17

2018: Communication Requirements by State



Rev. 09/11/18

Early Criticisms of U.S. Substitution Legislation

- Legislation premature? There are NO biosimilars in the United States marketplace.
- Premature laws create confusing patchwork of state substitution laws.
- Could legislation undermine public confidence in biosimilar medicines?

- First biosimilar approved March 6, 2015. Now 12 approved, 4 on market, and PBMs are switching patients.
- Pharmacists, physicians need to work together to educate lawmakers in remaining states, extend a common standard for these laws.
- To the contrary, Physicians defaulting to "do not substitute" as only means of knowing what patient is receiving would undermine biosimilar adoption.

Initial Resistance from Pharmacists

- Additionally, many **state pharmacy societies** had concerns that the word "notify" implied they were subservient to physicians, and preferred the word "communicate", which implies collaboration.
- **Pharmacies** also considered the initial timeframe allotted for notification, and the length of the record-keeping provisions to be onerous.
- While helping patients and physicians, bills also **empower pharmacists** to offer lower-cost alternatives to patients without seeking authorization from physicians.
- Yet as they were made aware of the benefits the communication provisions offer to patients, they have dropped their opposition and the legislation passed.

Today automatic substitution **faded as an issue of debate** among the two national pharmacy societies, ASHP and APhA.

Physician/Pharmacist Collaboration is Key

- Physicians have the authority to specify **"do not substitute"** for biological products and that specification overrides any policy – e.g. by payers or state law – that would have substitution be the standard or default practice.
- Physicians and pharmacists should **work collaboratively** to ensure that the treating physician is aware of the exact biologic – by manufacturer – given to a patient in order to facilitate patient care and accurate attribution of any adverse events that may occurs.

Common Ground Between Physicians and Pharmacists

- Both healthcare providers, who share concern for our patients
- Both experienced with and knowledgeable about medications
- Both incentivized to perform good pharmacovigilance
- Both want a good track-and-trace system for adverse events
- Both support good record keeping.

Collaboration among Pharmacists, Physicians, Manufacturers on substitution bills has resulted in improved legislation

2013 Bill Language		2016-Present Bill Language
"Notification"	→	**"Communication"**
Notification **only if biosimilar substituted**	→	Communication of which biologic was was dispensed- **innovator / biosimilar**
72 hours to notify	→	**5 days** to communicate
Must retain records for **5 years**	→	Must retain records for **2 years**

Timing of Communication

- The timing of the communication process must not impose an undue burden on the pharmacist
- Communication of a substitution is after dispensing
- Must be timely enough to facilitate **accurate record keeping** and **attribution of adverse events** by the physician.

Medication-use system

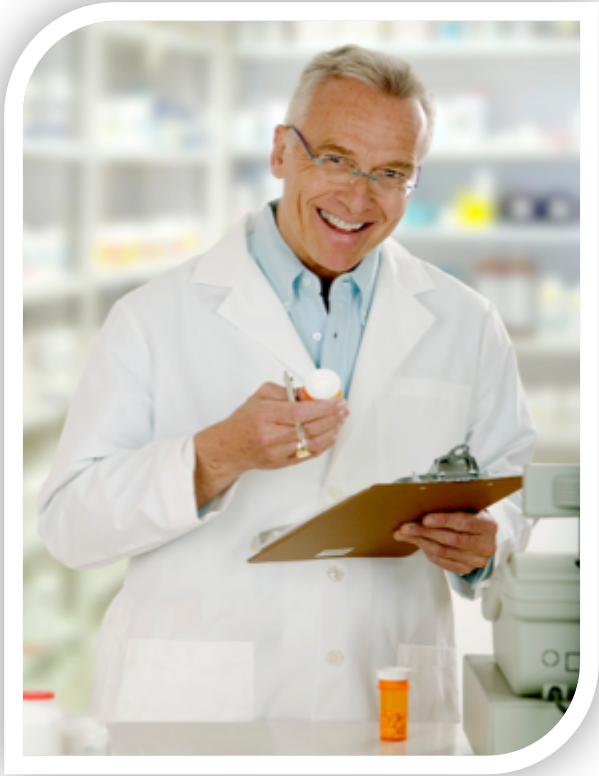
- Prescribing
- Preparation
- Dispensing
- Administration
- Monitoring

Strategies for Improving Prescribing

- Collaborative practice that includes a pharmacist
- The formulary system
- Therapeutic interchange (NOT substitution)
- Evidence-based clinical practice guidelines
- Clinical decision support systems
- Metrics and performance management
  - Effectiveness
  - Safety
  - Cost

Added Value of Pharmacists

- Prudent purchasing
- Inventory control
- Managing waste
- Managing utilization
- “Balanced scorecard” (pharmacoeconomics)
- Proactive awareness



Conclusions

- The pharmacist's responsibility does not end with the patient.
- As with vaccinations, it is a matter of responsibility to a larger community.
- Pharmacists have a larger responsibility to work collaboratively with physicians, regulators, manufacturers and others to create a strong pharmacovigilance system to protect everyone.
- Clear communication between all parties is essential for the successful rollout of biosimilars- not only in their naming, and also when they are substituted.

Thank You
For Your Attention