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PRN OPINION PAPER

Formulary management challenges and opportunities: 2020 and beyond - an opinion paper of the drug information practice and research network of the American College of Clinical Pharmacy

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Abstract

Formulary management systems in hospitals and health-systems serve to ensure that medications are rigorously evaluated for efficacy, safety, and value. The increased complexity of these systems, along with the broadening of items for formulary inclusion, poses unique challenges and opportunities for the development of innovative formulary management processes. Pharmacists are challenged to evaluate different types of medications that are not all small molecule entities as well as deal with medication shortages that can impact patient care. The authors review unique formulary aspects of biosimilars, gene therapy, rare disease treatments, outpatient therapies, and formulary-related challenges/opportunities with drug shortages. Core strategies for formulary management and drug shortage mitigation techniques in closed formulary settings are discussed. This information is intended to guide formulary decision-makers and other clinicians to effectively manage health-system formularies in 2020 and beyond.

KEYWORDS

cost-benefit analysis, evidence-based medicine, health care systems, pharmacy, safety

Formularies have evolved from humble beginnings as small, standardized lists of medications stocked in medication chests during the United States (U.S.) Revolutionary War[1] to the continually updated lists of medications and related information representing the clinical judgment of pharmacists, physicians, and other experts in the diagnosis/treatment of disease and promotion of health.[2] Formulary management systems serve to ensure that efficacy, safety, and value are rigorously evaluated for each medication requested for formulary addition.

Specific formulary categories and topics were identified as being relevant for discussion based on the expert opinion of the Drug Information Practice and Research Network (DI PRN) membership,

This paper represents the opinion of the Drug Information Practice and Research Network (DI PRN) of the American College of Clinical Pharmacy (ACCP). It does not necessarily represent an official ACCP commentary, guideline, or statement of policy or position.

although the authors recognize that unique formulary challenges also apply to radiopharmaceuticals, radiologic contrast agents, medical devices, herbal products, homeopathic products, aromatherapy products, and medical devices when used for therapeutic effect, which will not be reviewed in this article. This information is intended to provide guidance for formulary decision-makers, as well as frontline clinicians, to effectively manage hospital and health-system formularies in 2020 and beyond. We discuss advances in medication management that have a unique impact on formularies and Pharmacy & Therapeutics (P&T) committee decision-makers and can have a direct impact on patient care, safety, and the financial stability of hospitals and health-systems. The rapidly changing pipeline of drug discovery has provided improved clinical outcomes as well as changing the view of small molecule medications as the only therapeutic option. The unique formulary aspects of biosimilars, gene therapies, outpatient therapies, rare disease treatments, and drug shortages are discussed, with attention to innovative strategies for formulary management and drug shortage mitigation techniques in closed formulary settings.

1 | BIOSIMILARS

Biologic drugs, such as hormones, cytokines, clotting factors, and monoclonal antibodies, that are produced by living cells comprise a significant proportion of the U.S. pharmaceutical market. Biologics also represent a growing proportion of new drug approvals each decade. The expense of these products represents about 40% of total U.S. drug expenditure.[3] The high cost and growing market share of biologics make these products important targets for managing formularies and drug costs in the 21st century.

Biologics are complex molecules that exhibit structural differences (microheterogeneity), making it difficult to produce an exact copy, which historically protected biologics from competition from follow-on biologics, unlike the scenario with small molecule drugs and generic competition.[4] The Patient Protection and Affordable Care Act created the biosimilar approval pathway to generate competition and lower costs through "generic" biologics or biosimilars. Biosimilars are biologic drugs that are highly similar to the reference (brand) biologic product but may have minor structural differences in nonactive components of the molecule. Biosimilars do not have clinically meaningful differences from the reference biologic product (safety, purity, or potency). Food and Drug Administration (FDA) approval of a biosimilar largely comprises structural characterization, pharmacokinetic and pharmacodynamic studies, immunogenicity data, and clinical trial(s). Biosimilars may also be approved as interchangeable, which require additional studies that demonstrate continued efficacy and safety after alternating between biosimilar and reference biologic products several times.[5] There are currently no interchangeable biosimilars approved by the FDA (Table 1). Refer to the FDA Purple Book[6] for the most current biosimilar approval information and information on biosimilar interchangeability.

The use of biosimilars is expected to create significant cost savings, with some authors suggesting that biosimilar conversions may lead to health-system cost savings between $24 and $150 billion between 2017 and 2026.[7] However, the availability and use of biosimilars remain low within many hospital systems and preferred drug lists.

Multiple strategies may be utilized to leverage biosimilars on health-system formularies. The strictest strategies may select a single preferred or formulary biosimilar product. Others may select a small subset of products for inclusion on the formulary or a strategy of all products. Institutions may also decide to relegate the use of biosimilars to certain indications or use or populations (eg, FDA-labeled indications or any FDA-labeled indications from the reference product). Biosimilars should be reviewed for formulary addition at P&T committees per published guidance, which includes a review of efficacy, safety, cost, and operational considerations.[8,9] Biosimilar reviews should focus on data that demonstrate biosimilarity and, in particular, the comparative immunogenicity.[10,11] Biosimilar guidance from the FDA also allows for biosimilars to develop different delivery forms (eg, autoinjectors) and therefore different dosage forms. Related convenience, operational, and financial considerations should be considered during formulary review and determination of organizational strategy.[12,13]

Some hospital systems have implemented protocols to substitute reference products for a biosimilar product. These protocols should be individually reviewed to determine potential risks associated with multiple instances of product switching at admission and discharge from the hospital (or lack thereof). Similarly, some hospital systems have developed scoring tools based on clinical data to help guide evaluation of the appropriateness to substitute a biosimilar product. These tools may provide insight or structured evaluations of biosimilar products, but currently lack published evaluations of validity and accuracy.

P&T committees opting to begin using a biosimilar must determine how to manage current therapies. Many of these biologic products are utilized for chronic conditions or as part of a finite, but prolonged therapy. P&T-approved protocols may require a one-time switch to the new formulary biologic product, also known as nonmedical switching. Other decisions may allow established patients to be "grandfathered" into continuing their ongoing regimen with the previous biologic indefinitely. This strategy can detract from the benefits of biosimilars, particularly in diseases where initiation of therapy may represent only 20% or less of total use. The costs of enforcing a switch should also be considered, including operational costs, education costs, and prescriber costs. Some authors have suggested that a change to a biosimilar may cost more than the potential savings, although these comments are not well-founded in a clinical trial or real-world data.

P&T committees must consider unique challenges with the use of biosimilar products, including financial, efficacy, safety, and educational considerations. These challenges have likely contributed to low uptake and use of biosimilars in health-systems (Table 2). For example, rituximab is used for a variety of off-label indications that are not considered as part of FDA approval of a biosimilar. The immunogenic potential may be increased from multiple switches and should be considered when P&T committees determine how biosimilars will be used

TABLE 1 Approved and available biosimilars in the United States at beginning of 2020 (see reference 6[a])

Biologic	Approved biosimilars	Available biosimilars	Interchangeable biosimilars
Adalimumab	5	0	0
Bevacizumab	2	2	0
Epoetin alfa	1	1	0
Etanercept	2	0	0
Filgrastim	2	2	0
Infliximab	4	2	0
Pegfilgrastim	3	2	0
Rituximab	2	1	0
Trastuzumab	5	2	0

[a]Refer to reference 6 for current biosimilar approval information.

during hospitalizations or through multiple changes to preferred biologic products over time. Despite these concerns, aggregate real-world and randomized controlled trial data on biologics with high immunogenic potential do not support an increase in immunogenicity from the use of biosimilars or nonmedical switching.[11] Also, P&T committees must review these additional types of extrapolation individually, as the risks and benefits of extrapolation are not equal for each scenario.

TABLE 2 Unique challenges and considerations for evaluating biosimilars

Challenge or consideration	Description
Cost	• Rebates, contract prices, and overlay agreements
Reimbursement	• Brand-neutral reimbursement from CMS • Pass-through status for 340b drugs
Clinical guidelines	• Recommendations for (or against) use of biosimilars • Recommendations for off-label uses
Extrapolated indications	• Evaluate reasons for missing indications (eg, protection via Orphan Drug Act)
Extrapolated ancillary information	• Evaluate the extrapolation of off-label stability and compatibility • Evaluate extrapolation of off-label administration protocols (eg, infusion rates) • Evaluate the extrapolation of therapeutic drug monitoring
Interchangeable status	• Evaluate FDA-approved status • Consider nonmedical switching during hospitalizations according to therapeutic interchanges
Immunogenicity	• Evaluate immunogenicity data from single or multiple switches
Informatics	• Evaluate differentiation within formularies and electronic health records
Education	• Evaluate prescriber and pharmacist knowledge and understanding of biosimilars • Educate patients to prevent the nocebo effect

Abbreviations: CMS, Centers for Medicare and Medicaid Services; FDA, United States Food and Drug Administration.

Formulary management of biologics and biosimilars will be an important part of cost containment strategies over the coming decades. Despite slow uptake, FDA approval and use of biosimilars continue to grow. The biosimilar landscape has already transformed significantly since the first FDA approval, including new strategies for coding and Medicare recognition of biosimilars as branded products.

The FDA has committed to improving the clarity and ease of submitting for FDA approval, such as creating an Office of Therapeutic Biologics and Biosimilars, creating educational materials, and creating several guidance documents. These actions are likely to support the continued expansion of the number of reference products with biosimilar competition and increase the number of biosimilars per reference product. Also, the FDA deemed many biologic products that were not approved via a Biologics License Application (eg, insulin) as eligible for the development and approval of biosimilar and interchangeable products. This will continue to expand the approval of biosimilar products. The FDA has also suggested a change to significantly limit the amount of FDA review materials (eg, Chemistry Reviews, Medical Reviews) that are published, which will reduce structural, pharmacodynamic, immunogenic, and clinical data on biosimilars that are available for review.

P&T committees may take several actions to further realize the benefits of biosimilar products and should evaluate and integrate the use of biosimilars whenever possible. P&T committees should focus on the evaluation of extrapolated data, indications, and uses, particularly those that are not reviewed by the FDA. Collaboration between payers, hospital systems, and prescribers will also be important in realizing the benefits of biosimilars. This will help align formulary or preferred biosimilar products and establish confidence in the reimbursement for biosimilars. Removing administrative burdens that promote the use of lower cost biosimilar products will also help encourage the use of biosimilars. This collaboration may also allow innovative strategies to create shared biosimilar savings between payers and hospital systems.[14] These collaborations should balance short-term cost savings from aggressive contracting for preferred biosimilars and the ability of systems to be agile and share in cost savings.

As the market continues to grow, systems must consider the burden of supply chain management and inventory management at hospital systems (eg, it may not be feasible to stock and dispense many different biosimilars for an individual reference product).

P&T committees will also need to heavily consider the value of patient conveniences in evaluating biosimilars. Many biologics that are currently open to competition by biosimilars are also available in alternative forms that do not provide direct clinical benefits but provide other advantages. The alternatives may provide different routes, FDA approved use(s), different delivery devices, different frequencies, or other desirable properties. However, these alternatives may not compete directly with a biosimilar and may cost much more than the biosimilar as reference biologics.

P&T committees should also support education efforts for prescribers, pharmacists, and patients. Although few studies have evaluated the systemic impact of education on biosimilars, it is reasonable to expect that attitudes and practices with biosimilars will change with education.[15] These education efforts should underscore the FDA approval process, including the purpose and intent of structural studies, the presence of clinical and immunogenicity studies, and ongoing postmarketing safety monitoring. Prescribers should also be educated about the potential for structural differences between batches of biologic manufacturing, including changes to reference products, over time.

P&T committees must consider additional aspects of formulary management that extend to outpatient therapies, such as biosimilars. Outpatient use of medications is important to include within the hospital system formulary and includes employee prescription benefit plan design, outpatient infusion, home infusion, and other outpatient services. Health-systems may develop preferred medications, formulary restrictions, and therapeutic interchanges or protocols for drug use in outpatient settings. These practices may further improve cost savings and support contract negotiations, which are critical practices as health care shifts from volume-based to value-based care.

2 | RARE DISEASE TREATMENTS

Out of a total of 5.8 billion prescriptions dispensed in the U.S. in 2018, specialty medications accounted for 2.2% of all prescription volume, yet contributed to nearly 50% of the total yearly drug spend.[16] Specialty medications have complexities associated with one or more of the following that may require additional support services: the disease, drug, administration, safety, monitoring, distribution, and/or fiscal responsibility.[17] In 2017, the annual retail cost of therapy for a specialty medication averaged $78 871, while the average annual cost of an orphan drug was $87 319.[18] Generally, as the size of the patient population decreases, the cost per treatment increases; thus, ultra-rare gene therapies are the most expensive. Approximately 87% of orphan drugs are considered specialty medications.[19] Orphan drugs are used for rare diseases, defined as a disease that affects less than 200 000 people in the U.S.[20] The FDA has incentivized the development of rare disease treatments through the Orphan Drug Act by granting market exclusivity for 7 years, providing tax credits, and waiving the prescription user drug fee (estimated at $3 million).

Rare diseases may vary in clinical presentation; some patients have an active disease with episodes resulting in health care visits or signs of irreversible damage while others are asymptomatic. With the cost of therapy at a premium ($0.5 million to $1 million annually), it is challenging to determine which patients should qualify for treatment with limited evidence to support use in asymptomatic patients. The risks and benefits of treatment must be carefully considered, as well as the possibility of damage from the disease course. This issue exists with rare disease treatments because alternative treatments may not be available and genetic testing can identify the presence of disease before signs of disease activity.

The FDA has received over 900 investigational new drug (IND) applications for gene therapies and 4 are currently available.[21] The first three gene therapies were approved in 2017 (ie, tisagenlecleucel, axicabtagene ciloleucel, and voretigene neparvovec-rzyl) and the costliest therapy ($2.1 million per treatment) was introduced in 2019 (onasemnogene abeparvovec-xioi). Gene therapy may be introduced either in vivo (directly into the patient) or ex vivo (extraction, modified, and reintroduction).[22] The treatment works to establish normal function by replacing or inactivating a dysfunctional gene, or by the introduction of a new or modified gene. Gene therapy may be introduced by plasmid DNA, viral vectors, bacterial vectors, human gene editing, or cellular gene therapy derived from a patient. Risks of delayed adverse events are higher with gene therapy products that modify the host genome, which includes integrating vectors (eg, gammaretrovirus, lentivirus, foamy virus), latency reactivation of herpesvirus, and genome-editing products.[23] The vectors can persist over the life of the patient's transduced cells and the long-term follow-up period may be as long as 15 years for gene therapy modifying the host genome due to the risk of malignancy, severe infection, or autoimmune disease.

The FDA released six guidance documents to industry for cellular and gene therapies regarding chemistry, manufacturing, control, IND applications, long-term follow-up, testing of retroviral vector gene therapy, and specific guidance for hemophilia, rare diseases, and retinal disorders.[24] In the guidance document of gene therapy for a rare disease, the FDA addresses complexities of developing rare disease gene therapy medications due to limited study population sizes, the variability of disease clinical manifestations/progression, and the uncertain long-term safety or durability.[24,25] The document also notes that while a randomized controlled trial is ideal, it may not be feasible in small population studies and a single-arm trial with either a historical control or historical observation period may be necessary. It is the opinion of the ACCP DI PRN that a number of unanswered questions associated with gene therapy exist (Table 3).

Formulary challenges of relevance to rare disease treatments include institutional access to medication (whether negotiated to be direct access or indirect access through white-, brown-, or clear-bagging), high cost, and low-patient volume. These challenges may be overcome through thoughtful value analysis within the formulary structure/perspective, direct manufacturer contracting to ensure

access to medication, and a quality monitoring structure suitable for enhanced side effect/risk evaluation and mitigation strategy (REMS) criteria monitoring as well as outcomes measurement.

Value-based contracts (VBC) have emerged as a result of the increased cost of care associated with treatments for rare diseases and gene therapies. In a VBC, the manufacturer agrees to provide reimbursement to the payer (up to the allowable threshold based on health plan) and patient (for copays) if the treatment is unsuccessful. Contracts typically require appropriate diagnostics (eg, genetic or biomarker testing) and assessment of treatment failure over a defined period (eg, disease progression, use of preventative medications, hospitalization). Contracting with the patient may be necessary to agree to maintain communications for monitoring to occur. P&T committees should consider the VBC terms and ongoing monitoring commitments when evaluating rare disease items for formulary addition.

Outpatient formulary management involves additional complexity, implementation, and enforcement challenges. P&T committees should review payer outpatient coverage of these therapies when considering the formulary addition of new medications. This may also include reviewing and appealing Medicare national and local coverage determinations.[26] Hospital systems must also consider the site of care restrictions that preferentially require administration of medications at lower-cost physician offices over outpatient hospital facilities. These activities must be supported by the appropriate infrastructure to determine payer coverage before the administration of medications.

Limited distribution models and payer restrictions have also increased the number of outpatient therapies that are not obtained via traditional methods.[27] Brown bagging (a scenario where medication is supplied directly to the patient, who brings it to a health care facility for injection/infusion), white bagging (a scenario where medication is supplied directly by a specialty pharmacy to a health care facility for a specific patient), and clear bagging (a scenario where a health-system's own specialty pharmacy supplies medication directly within the health-system for injection/infusion) all disrupt usual hospital system medication supply chains. These present additional challenges to managing these medications, while reducing the reimbursement at the hospital pharmacy that prepares, dispenses, and administers the medication that must be considered when determining the formulary status of outpatient therapies. Additional financial opportunities and formulary management efficiencies may be present for health-systems that elect to own/operate a specialty pharmacy.

Outpatient therapies and related formulary management practices represent additional opportunities to collaborate with payers to develop mutually beneficial practices including aligned formulary statuses and criteria for use. This also presents an opportunity to develop an innovative model for payment of high-cost outpatient therapies. Hospital systems and payers may be able to create new value-based, outcome-based, or other innovative reimbursement agreements around outpatient therapies.

TABLE 3 Unique formulary management questions—gene therapy

- What is the outcome or durability of the response?
  - If a patient receives a one-time gene therapy treatment, when will alternative treatments be needed in the future?
  - If the patient does not consider a change in baseline function to be of value, or not considered "normal" after gene therapy, will prescribers continue treating with alternative treatment?
  - If there is a lack of confidence in beneficial treatment outcomes (eg, reduction in bleeds, hospitalization), will preventative medications be prescribed in anticipation of failure, increasing the total cost associated with treatment?
- What is the long-term safety of gene therapy?
  - What unintended consequences may arise as a result of gene therapy (eg, malignancy, infections, autoimmune disease)?
  - How will the lifelong safety of gene therapy be assessed if the treated patient no longer maintains contact with the specialist involved with their disease?
- What are the considerations regarding cost or reimbursement?
  - Who is held accountable if gene therapy is dispensed and the patient does not show up for treatment (medication cannot be reused)?
  - If gene therapies gain approval for more prevalent diseases, will the cost of treatment be adjusted to a more affordable rate?
  - How will payers respond to the use of gene therapy? Will it be used preferentially over a lifelong treatment alternative?
  - What will the patient's financial responsibility be for gene therapy and will patient-assistance programs be available for a one-time treatment?
  - If two products are considered equivalent and one offers a value-based contract but is more expensive, which product will be preferred?
- What other impacts should be considered?
  - If gene therapy eliminates the need for specialized care of a condition, how will health-systems and clinics be impacted?
  - What is the pharmacist's role in the management of gene therapy?
  - Will patients consider treatment with gene therapy if their disease is controlled by alternative medications?

3 | DRUG SHORTAGES AND MANAGEMENT STRATEGIES IN CLOSED FORMULARIES

Pharmaceutical drug shortages (PDS) are a growing epidemic, which impact economic growth, the quality of patient care, and cause operational disruptions. In 2019, 166 new drug shortages were reported by the FDA, 39% of which were for injectables.[28] PDS is a significant public health crisis that affects the continuum of health care including the medication supply chain, health-systems, and patient care, as well as the increased cost of labor associated with managing the problem. In a 2019 survey of over 6000 health-systems, the annualized cost of labor to manage PDS was estimated at $359 million per year. This was attributed to time for additional staffing, loss of revenue from delay or cancelled care, or time spent on updating information technology.[29]

When PDS occur in closed formulary settings, a chain of events is initiated having an impact on both operational and therapeutic activities. Institutions may operate with a "just in time inventory" for high cost and potentially other formulary items—this formulary and cost

management strategy may be problematic in the setting of PDS. Managing PDS is a complex challenge. The common tasks that require pharmacy input and management are listed in Table 4.[30,31]

A key guidance document from the American Society of Health-System Pharmacists (ASHP) serves as a framework for a stepwise plan and a hierarchical process involving both operational and therapeutic assessments.[30] ASHP outlines factors impacting PDS with a major concern of patient safety, which is key in closed formulary settings when planning for PDS. ASHP stresses the importance of various teams to analyze situations and determine best practices for the institution. This includes considering therapeutic formulary alternatives when PDS impacts patient care. The document splits shortage plans into two divisions: operational and therapeutic assessments. The creation of a short-term impact analysis is recommended to estimate the risk of the PDS on patient care. It is recommended to communicate and be transparent to all parties involved in the process and to successfully implement the plan at all stages.

ASHP recognizes the need for inventory system changes as part of drug shortage mitigation in closed formulary settings. This includes refraining from unnecessarily stockpiling medications, which may prevent the appearance of artificial shortages, as well as result in a need to maintain costly inventory. The SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2 [COVID-19]) outbreak has provided a recent example of the damages of stockpiling inventory related to personal protective equipment, medications, and ventilators.[32] Congress has responded with the passage of the Coronavirus Aid, Relief, and Economic Security (CARES) Act, which strengthens the PDS language for the FDA and manufacturers.[33]

In a closed formulary system, handling drug shortages requires two key elements: timely communication and a shift in operational protocols. Examples of proactive measures that can be taken by institutions with a closed formulary system to prevent and mitigate drug shortages are summarized below.

Training and education are key components for handling a sudden change in PDS. Pharmacy personnel training in technology, automation, communication, and the identification of early-warning signals for drug shortages is recommended. The latter includes the use of the FDA and the ASHP websites to manage drug shortages. ASHP recommends familiarizing the pharmacy and clinical staff to the protocols that will help strategically in handling drug shortages. Drug shortage management steps should be adjusted to fit the specific needs of each institution.[30]

Establishing an institution-specific, multidisciplinary drug shortage team involving members from administration, information technology, clinical (eg, nursing, medical, P&T committee), and pharmacy is another strategy to handle the complex drug shortage issue. This team must monitor and report shortages related to the closed formulary and communicate it to institutional departments. Therapeutic interchange is another strategy used frequently to handle drug shortages; this may require P&T committee approval to distribute the alternate

TABLE 4 Strategies on managing pharmaceutical drug shortages (PDS) within closed formularies in health-systems

Strategies	Examples
Awareness and appointment of key PDS management personnel and resources	• Pharmacy and other institutional resources needed to manage drug shortages
	• Devise a hospital-specific shortage management plan/policy incorporating recommendations from ASHP's "Guidelines on Managing Drug Shortages"[30]
Awareness of key PDS resources	• Identify and enhance awareness of key resources for managing PDS including ASHP and FDA's drug shortages websites, hospital's affiliation agreements with GPOs, direct manufacturers agreements if established, and affiliate health-systems (borrowing, buying, trading)
Employ effective and consistent communication practices	• Identify key stakeholders to form open communication of PDS and potential solutions
	• Establish methods of communicating new and existing PDS or recalls to pharmacy administration to tracks trends and formulate advanced planning
	• Determine appropriate venues for communicating PDS updates, solutions, education opportunities, and risk mitigation strategies resulting from PDS
	• Determine a standard of frequency for communicating real-time PDS to relevant parties
	• Evaluate feedback from key stakeholders on pharmacy's management of the PDS program and identify opportunities for improvement of handling PDS
Leverage health information technology (HIT)	• Develop implementation strategies to rapidly and regularly update health information systems' technology regarding PDS
	• Establish best practices for updating HIT to reduce the burden of time to identify PDS and alternative options, reduce medication errors due to package size selection, dose, or concentration differences, and implement technological changes (eg, barcoding)

Abbreviations: ASHP, American Society of Health-System Pharmacists; FDA, United States Food and Drug Administration; GPO, Group Purchasing Organization.

drug for patient care. Having advanced approval or understanding for alternate drug use will help in the procurement of drugs and the ability to maintain a closed formulary during PDS.

Clinicians can be helpful in reducing the impact of drug shortages through standardization of care by adhering to clinical guidelines and tailoring care to the individual. They can help select available alternatives, which may involve the use of unfamiliar drugs or unfamiliar therapy from another specialty. Proactively educating or collaborating with other clinicians in another specialty will help in managing drug shortages in a closed formulary system.

Educating pharmacy and clinical personnel about the alternative drug(s) to be used in case of shortage(s) and posting both the clinical and operational formulary management information on the institution intranet for easy retrieval and training on critical information will help to minimize the negative outcomes associated with alternate medication use. Clinical decision support (CDS) system tools may be of help at the point of service by reminding prescribers of the formulary alternatives available as a means to mitigate drug shortages and the incurred cost.

Despite legislative and professional organizations' efforts, drug shortages are still an everyday problem which impact both health care professionals and society. The impact of global involvement with PDS cannot be understated as pharmacies witness the disruption of the supply chain due to the COVID-19 pandemic. Current FDA and ASHP mitigation strategies as summarized in Table 4 are helpful, but continued efforts to improve the drug supply chain and maintain access to safe/effective therapies are essential within closed formulary settings.

4 | INNOVATIVE METHODS OF FORMULARY MANAGEMENT

Formulary management strategies have evolved to address these new challenges, including the creation of detailed criteria for review of off-label use of formulary medications,[34] review of specific medication types (gene therapy, biosimilars), specialty medications, clinical and operational strategies for cost containment, CDS, and lean six sigma models for integration of new formulary additions.[35] We will discuss value-based formularies, CDS, and high-cost medication stewardship as potential solutions to the various challenges presented.

4.1 | Value-Based Formularies

The assessment of medication value is a logical extension of the traditional assessment of cost in the formulary management process. The increasing cost of medications has resulted in a broadening of formulary categories (Table 5) as well as creative solutions to mitigate their financial impact using different pharmacoeconomic models (eg, cost-minimization, cost utility) as relevant to the drug/disease state.[36] Five value frameworks exist within the oncology landscape, which share a focus on safety and survival but demonstrate variability in methodology and perspective in comparing value as well as framework-specific advantages and disadvantages.[37] One health-system implemented a value-based approach toward formulary management of specialty medications that includes scored criteria for the assessment of efficacy, risk, cost, and societal benefit.[38] Value is shaped by the perspective of the various decisionmakers, which may or may not be aligned in terms of each party's respective willingness to pay[39,40] and may or may not reflect a truly waste-free formulary[41] as a result. Value-based formularies have been described in the literature for health-systems[38] as well as payors[42] and may represent an innovative formulary management opportunity. Advantages include the assessment of value vs cost and promotion of high-value care in the formulary process. Disadvantages include varying perspectives on willingness to pay and the potential to limit outpatient formulary availability of potentially reimbursable therapies considered to be lower value by the organization.

4.2 | Clinical Decision Support in Formulary Management

CDS encompasses a set of tools that assist the prescriber with patient-specific knowledge to aid in decision-making to enhance health care.[43,44] CDS, as a part of computerized prescriber order entry (CPOE) systems, is a tool that guides prescribing practices to align with an institutional formulary and can be a powerful formulary management tool when properly designed/implemented. The institutional formulary includes medications that have been reviewed by the P&T committee for their safety, efficacy, and cost-effectiveness. CDS tools can be utilized as a mechanism for therapeutic interchanges, best practice alerts, and standardized dosing to assist with increasing formulary adherence[45] and/or serve as the gatekeeper to ensure that all REMS requirements are followed to ensure safe medication use.[44] The potential for CDS to drive institutional formulary adherence and free up pharmacist's time for other clinical activities are recognized benefits.[43]

CDS provides guidance that can either be active or passive. Passive CDS requires the user to perform an action to receive guidance.[46,47] For instance, selecting an order set that contains the institutional formulary medications, which would enhance formulary adherence, or using an electronic template in an electronic health record (EHR). Examples of active CDS involve the use of best practice alerts and therapeutic interchanges. Therapeutic interchange is a formulary management strategy used to decrease the number of medications maintained on the drug formulary. Drug classes that contain several similar medications are best suited for therapeutic interchanges. The use of therapeutic interchange protocols allows the verifying pharmacist to automatically change the prescribing medication to the preferred formulary alternative.[43]

In addition, active CDS promotes formulary adherence by using best practice alerts. When a prescriber enters an order for a nonformulary medication, active CDS can recommend a formulary alternative or ask the prescriber to provide a rationale for the use of the nonformulary medication. For example, a large academic medical

TABLE 5 Potential formulary categories

Formulary category	Stocked?	Restricted?	Example(s)
Formulary	Yes	No	Routinely available medications in a facility
Formulary, provisional	Yes	Yes or No	Medications that may receive limited approval for pilot use for a specific time, with or without specific data collection, and reporting requirements to the P&T committee
Formulary, criteria for use	Yes	Yes	Medications with specific institutional usage criteria, REMS, suitable for prescribing only by specific prescribers or prescriber specialties
Formulary, nonstocked	No	Yes	Low use and/or high-cost medications, medications with distribution restrictions, medications requiring the use of patient's supply, medications deemed appropriate to obtain through clear, white, or brown-bagging, medications obtained via consignment, regional resource sharing
Formulary, outpatient	Yes	Yes	Medications limited to outpatient (eg, clinic, infusion center) areas and/or requiring confirmation of benefits or coverage before use
Nonformulary	No	Yes	Items that have not been evaluated for formulary inclusion but may be available in certain circumstances to order via organizational non-formulary processes.
Nonformulary, Nonstocked	No	Yes	Items that have been evaluated for formulary inclusion, denied, and determined to not be appropriate for an individual prescriber non-formulary override request under most normal circumstances

Abbreviations: P&T, Pharmacy & Therapeutics; REMS, risk evaluation and mitigation strategies.

center evaluated the frequency of nonformulary medication override alerts to improve formulary adherence by reducing the number of inappropriate nonformulary alert overrides. Her and colleagues[48] reviewed 206 nonformulary overrides consisting of the top 11 high cost and frequently prescribed medications at the institution. The results demonstrated that approximately 20% of the overrides were inappropriate and the most common reason for overrides was the failure to use the formulary alternatives before requesting nonformulary medications.

Although active CDS can be beneficial, overuse of best practice alerts can result in alert fatigue and increased formulary nonadherence.[45] Alert fatigue occurs when the prescriber is inundated with numerous alerts from the CDS and becomes desensitized to the importance of the alerts. Strategies to decrease inappropriate overrides include combining multiple alerts, reducing the number of alerts by only allowing higher severity alerts, and by evaluating the decision tree or logic in the CDS to decrease the frequency of alert triggers.[46]

4.3 | High-cost medication stewardship

High costs are not only associated with novel medications that target rare, chronic, and specialty disease states to which minimal alternative therapies exist, but also reflect the impact of drug shortages, industry consolidations, or pharmaceutical companies increasing medication prices to what the market is willing to bear.[49]

The increase in high-cost medications on the market coupled with decreased reimbursement has led to increased scrutiny of the use of these medications. Over time, stewardship of high-cost medication use has become a necessary component of formulary management. Existing formulary strategies to control high-cost medication use include, but are not limited to, designation as nonformulary, restricted ability to order, therapeutic interchange, and restrictions by indication or site of care (Table 6). Historically, this was accomplished through the P&T committee formulary approval process. P&T committees, however, may lack the ability to be nimble and address urgent patient needs. The development of medication stewardship teams may help to lower medication costs, while also providing access to patients who require therapy.

Durvasula and colleagues[50] described the development of a high-cost medication review committee appointed to manage evidence-based review and approval of high-cost medication use requests. High-cost medications were defined as those greater than or equal to $5000 per dose or $10 000 for the course of therapy. The high-cost medication review committee developed standardized processes for review, criteria for use, and alerts in the EHR to communicate the need for approval. An on-call team composed of a physician and a pharmacist reviewed requests, utilizing available resources and patient-specific information to assess if the request met the threshold for approval. The request was denied if criteria was not met, with an opportunity for the prescriber to

TABLE 6 Key elements of high-cost medication stewardship

- Multidisciplinary engagement
- Evaluation of operations to improve the efficiency of review and approval of medication use
- Communication of requirements for high-cost medication use and approval process within the EHR at the point of prescribing
- Documented formulary preferred options where available
- Education to pharmacists and prescribers
- Assessment of financial risk and reimbursement
- Established outcomes tracking for each targeted high-cost medication
- Annual re-evaluation of high-cost medication program goals
- Ongoing surveillance of drug price increases, drug shortages, and other market disruptions that may impact utilization

Abbreviation: EHR, electronic health record.

appeal. If the prescriber appealed, it then escalated to the full committee for deliberation and decision. The focus on an evidence-based review from peers and colleagues strengthened the recommendation to approve or deny the request, putting the focus on patient need rather than simply cost. It also engaged frontline providers in being mindful of costs behind care, increased cost transparency, and reduced variation in care that may otherwise exist.

Blood factor products tend to be high-cost items ripe for opportunity for cost minimization efforts. Amerine and colleagues[51] described the implementation of a blood factor stewardship program after factor products were identified as a large contributor to drug expense. A committee of experts was assembled to review the primary literature, standardized treatment options available by designating one product per factor class, and developed guidelines for use. Pharmacists were charged with helping to ensure an appropriate choice of therapy, dosing, and achievement of target blood factor concentrations. By leveraging expertise, optimizing doses and/or frequencies to minimize waste, and promotion of system-wide education on blood factor use, the program realized $4 million in cost savings and improved patient outcomes.

Although these examples focus on the creation of high-cost medication oversight committees or programs, it is important to note that this approach may not fit all settings. The focus must be placed on areas of need for each institution; assessing opportunities to improve contracting efforts, reassessing purchasing practices, improving analytics to better track pricing trends and reimbursement, and communicating high cost medication criteria for use at the point of prescribing are all strategies that should be considered to keep costs manageable.

5 | CONCLUSION

As the health care landscape continues to evolve and larger numbers of novel therapies are approved, it will be imperative for organizations to continually assess processes and develop innovative approaches to make these therapies and products available when clinically indicated. A periodic review of published literature to identify, adapt, and apply innovative formulary management strategies for high cost agents is recommended. Biologics, biosimilars, and gene therapies are being FDA approved in increasing numbers and require pharmacists to stay current on the formulary issues that these novel agents create in managing patients. Some of these products go through closed distribution systems or involve risk management strategies with provider training. Biosimilars necessitate P&T committees to evaluate efficacy, safety, and cost to realize the benefits of these products and to provide direction to the institution on these therapies. P&T committees will need to consider both patient factors and provider education.

Pharmacists will be challenged with gene therapies as well as new modalities to treat some rare disease states. In addition to new therapy management challenges, pharmacists often are the health care providers who need to respond to drug shortages, which can create difficult situations. Guidance documents have been published that can help P&T committees effectively mitigate shortages and minimize impact on patient care. Several federal agencies, private entities, and legislative efforts are trying to address the factors that lead to drug shortages to help mitigate future shortages. New challenges require pharmacists to think differently about formularies and P&T committees. New tools include value-based formularies, CDS, and high cost mediation stewardship programs. These new and innovative strategies are imperative for effective formulary management going forward.

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CONFLICT OF INTEREST

Steven T. Johnson reports that he is a consultant and member of an advisory board for Coherus Biosciences, Inc. as well as an active speaker's bureau member for Coherus Biosciences, Inc. and Pfizer, Inc.; Krisy-Ann Thornby reports that her spouse is an employee of McKesson (U.S. Oncology Network). None of the remaining authors report any potential conflict of interest.

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REFERENCES

1. Mehr SM. The evolutionary role of the pharmacy and therapeutics committee in technology assessment. *Manag Care Interface*. 2006;19(1):42–45.
2. American Society of Health-System Pharmacists. ASHP statement on the pharmacy and therapeutics committee and the formulary system. *Am J Health-Syst Pharm*. 2008;65:2384–2386.
3. Sarpatwari A, Barenie R, Curfman G, Darrow JJ, Kesselheim AS. The US biosimilar market: stunted growth and possible reforms. *Clin Pharmacol Ther*. 2019;105(1):92–100.
4. Mehr SR, Zimmerman MP. Is a biologic produced 15 years ago a biosimilar of itself today? *Am Health Drug Benefits*. 2016;9(9):515–518.

5. US Food and Drug Administration. Department of Health and Human Services. [cited 2020 Aug 23] . Available from: https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars.
6. US Food and Drug Administration (FDA). Purple book: Lists of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations. [cited August 23, 2020]. https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/purple-book-lists-licensed-biological-products-reference-product-exclusivity-and-biosimilarity-or.
7. Mulcahy AW, Hlavka JP, Case SR. *Biosimilar cost savings in the United States: Initial experience and future potential*. Santa Monica, CA: RAND Corporation, 2017. [cited August 23, 2020]. https://www.rand.org/pubs/perspectives/PE264.html.
8. The AMCP format for formulary submissions. The AMCP format for formulary submissions: Welcome to version 4.0. *J Manag Care Spec Pharm*. 2016;22(5):444–446.
9. Tyler LS, Cole SW, May JR, et al. ASHP Expert Panel on Formulary Management. ASHP guidelines on the pharmacy and therapeutics committee and the formulary system. *Am J Health Syst Pharm*. 2008; 65:1272–1283.
10. Greene L, Singh RM, Carden MJ, Pardo CO, Lichtenstein GR. Strategies for overcoming barriers to adopting biosimilars and achieving goals of the biologics price competition and innovation act: A survey of managed care and specialty pharmacy professionals. *J Manag Care Spec Pharm*. 2019 Aug;25(8):904–912.
11. Martelli L, Peyrin-Biroulet L. efficacy, safety and immunogenicity of biosimilars in inflammatory bowel diseases: A systematic review. *Curr Med Chem*. 2019;26(2):270–279.
12. US Food and Drug Administration. Biosimilar action plan: Balancing innovation and competition 2018. [cited 2020 Aug 23]. Available from: https://www.fda.gov/media/114574/download.
13. US Food and Drug Administration. FDA works to ensure smooth regulatory transition of insulin and other biological products. 2020. [cited 2020 Aug 23]. Available from: https://www.fda.gov/news-events/press-announcements/fda-works-ensure-smooth-regulatory-transition-insulin-and-other-biological-products.
14. Manolis CH, Rajasenan K, Harwin W, McClelland S, Lopes M, Farnum C. Biosimilars: Opportunities to promote optimization through payer and prescriber collaboration. *J Manag Care Spec Pharm*. 2016;22(9):S3–S9.
15. Ismailov RM, Khasanova ZD. Biosimilar knowledge among oncology/hematology team members in Colorado, USA: An educational initiative and follow-up survey. *BioDrugs*. 2018 Oct;32(5):499–506.
16. IQVIA. Medicine use and spending in the U.S [cited 2020 Aug 23]. Available from: https://www.iqvia.com/insights/the-iqvia-institute/reports/medicine-use-and-spending-in-the-us-a-review-of-2018-and-outlook-to-2023.
17. National Association of Specialty Pharmacy Website. [cited 2020 Aug 23]. Available from: http://www.naspnet.org/wp-content/uploads/2017/02/NASP-Defintions-final-2.16.pdf.
18. AARP Public Policy Institute. Rx price watch report: Specialty prescription drug prices continue to climb. [cited 2020 Aug 23]. Available from: https://www.aarp.org/content/dam/aarp/ppi/2019/06/specialty-prescription-drug-prices-continue-to-climb.doi.10.26419-2Fppi.00073.002.pdf.
19. IQVIA. Orphan drugs in the US. 2018. [cited 2020 Aug 23]. Available from: https://www.iqvia.com/insights/the-iqvia-institute/reports/orphan-drugs-in-the-united-states-growth-trends-in-rare-disease-treatments.
20. U.S. Food and Drug Administration. Rare diseases at FDA. 2020. [cited 2020 Aug 23]. Available from: https://www.fda.gov/patients/rare-diseases-fda.
21. U.S. Food and Drug Administration. FDA news release: FDA continues strong support of innovation in development of gene therapy products. 2020. [cited 2020 Aug 23]. Available from: https://www.fda.gov/news-events/press-announcements/fda-continues-strong-support-innovation-development-gene-therapy-products.
22. U.S. Food and Drug Administration. What is gene therapy? [cited 2020 Aug 23]. Available from: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy.
23. U.S. Food and Drug Administration. Long term follow-up after administration of human gene therapy products. [cited 2020 Aug 23]. Available from: https://www.fda.gov/media/113768/download.
24. U.S. Food and Drug Administration. Cellular and gene therapy guidance. [cited 2020 Aug 23]. Available from: https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances.
25. U.S. Food and Drug Administration. Human gene therapy for rare disease. [cited 2020 Aug 23]. Available from: https://www.fda.gov/media/113807/download.
26. Heindel G, Smith J, Cruz J, Pappas A. Utilizing a drug information center for submitting reconsiderations for local coverage determinations. *Am J Health Syst Pharm*. 2017 Feb 1;74:106–107.
27. Pedersen CA, Schneider PJ, Ganio MC, Scheckelhoff DJ. ASHP national survey of pharmacy practice in hospital settings: Monitoring and patient education-2018. *Am J Health Syst Pharm*. 2019 Jul 2;76: 1038–1058.
28. Drug shortages statistics. National drug shortages: Annual new shortages by year. [cited 2020 Aug 23]. Available from: https://www.ashp.org/Drug-Shortages/Shortage-Resources/Drug-Shortages-Statistics.
29. Baumer AM, Clark AM, Witmer DR, Geize SB, Vermulen LC, Deffenbaugh JH. National survey of the impact of drug shortages in acute care hospitals. *Am J Health Syst Pharm*. 2004;61:2015–2022.
30. American Society of Health-System Pharmacists. ASHP Guidelines on Managing Drug Shortages. *Am J Health-Syst Pharm*. 2018;75: 1742–1750.
31. Fox E, Tyler L. One pharmacy's approach to managing drug shortages. *Am J Health-System Pharm*. 2003;60:27,31.
32. World Health Organization Report Shortage of personal protective equipment endangering health workers worldwide. [cited 2020 Aug 28]. https://www.who.int/news-room/detail/03-03-2020-shortage-of-personal-protective-equipment-endangering-health-workers-worldwide.
33. S.3548. CARES Act [cited 2020 Aug 23]. https://www.congress.gov/bill/116th-congress/senate-bill/3548/text.
34. Skledar SJ, Corman SL, Smitherman T. Addressing innovative off-label medication use at an academic medical center. *Am J Health-Syst Pharm*. 2015;72:469–477.
35. Sreedharan VR, Raju R. A systematic literature review of lean six sigma in different industries. *Intern J Lean Six Sigma*. 2016;7:430–466. https://doi.org/10.1108/IJLSS-12-2015-0050.
36. Heindel GA, McIntyre CM. Contemporary challenges and novel strategies for health-system formulary management. *Am J Health-Syst Pharm*. 2018;75:556–560.
37. Frois C, Howe A, Jarvis J, et al. Drug treatment value in a changing oncology landscape: A literature review and prescriber perspective. *J Manag Care Spec Pharm*. 2019;25(2):246–259.
38. Seigfried RJ, Corbo T, Saltzberg MT, Reitz J, Bennett DA. Deciding which drugs get onto the formulary: A value-based approach. *Value Health*. 2013;16:901–906.
39. Beveridge R, Fox J, Higgins SA, et al. Roundtable—the changing oncology landscape: Evolution or revolution? *J Natl Compr Canc Netw*. 2013 May;11(5.5):636–638.
40. Yeung K. Value-based insurance design: Current evidence and future directions. *J Manag Care Spec Pharm*. 2019;25(7):738.41.
41. Burns J. The few. The effective. The cheapest. The waste-free formulary. *Manag Care*. 2018 Aug;27(8):17–18.

42. Sullivan SD, Yeung K, Vogeler C, et al. Design, implementation, and first-year outcomes of a value-based drug formulary. *J Manag Care Spec Pharm*. 2015;21(4):269–275.
43. Helmons PF, Coates CR, Kosterink JG, Daniels CE. Decision support at the point of prescribing to increase formulary adherence. *Am J Health Syst Pharm*. 2015;72:408–413.
44. Raber JH. The formulary process from a risk management perspective. *Pharmacotherapy*. 2010;30(6 Pt 2):42S–47S.
45. Tolley CL, Slight SP, Husband AK, Watson N, Bates DW. Improving medication-related clinical decision support. *Am J Health-Syst Pharm*. 2018;75:239–246.
46. Wasylewicz ATM, Scheepers-Hoeks AMJW. Clinical decision support systems. In: Kubben P, Dumontier M, Dekker A, editors. *Fundamentals of clinical data science*. Cham: Springer, 2019. https://doi.org/10.1007/978-3-319-99713-1_11.
47. Bell GC, Crews KR, Wilkinson MR, et al. Development and use of active clinical decision support for preemptive pharmacogenomics. *J Am Med Inform Assoc*. 2014;21(e1):e93–e99. https://doi.org/10.1136/amiajnl-2013-001993.
48. Her QL, Amato MG, Seger DL, et al. The frequency of inappropriate nonformulary medication alert overrides in the inpatient setting. *J Am Med Inform Assoc*. 2016;23:924–933.
49. McConnell KJ, Guzman OE, Pherwani N, Spencer DD, Van Cura JD, Shea KM. Operational and clinical strategies to address drug cost containment in the acute care setting. *Pharmacotherapy*. 2017;37(1):25–35.
50. Durvasula R, Kelly J, Schleyer A, Anawalt BD, Somani S, Dellit TH. Standardized review and approval process for high-cost medication use promotes value-based care in a large academic medical system. *Am Health Drug Benefits*. 2018;11(2):65–73.
51. Amerine LB, Chen SL, Daniels R, Key N, Eckel SF, Savage SW. Impact of an innovative blood factor stewardship program on drug expense and patient care. *Am J Health Syst Pharm*. 2015;72:1579–1584.

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