

Life Sciences Mergers and Acquisitions: How Healthcare Reform Will Change Your Partnership Strategy



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Elsevier Business Intelligence Webinar

Impact on Regulatory Due Diligence for M&A/Partnering of Healthcare Reform Law

- Healthcare Reform Law (Patient Protection and Affordable Care Act of 2010, as amended by the Health Care Education Reconciliation Act of 2010) will significantly change regulatory due diligence for life sciences M&A/partnering.
- Most traditional areas of regulatory due diligence are affected
- Need now to incorporate in life sciences regulatory due diligence the significant impact on healthcare providers, *i.e.*, customers of product manufacturers
- Consequent substantial effects on, and uncertainty regarding, appropriate valuation of target products or companies

Assessing the Target's FDA AND CMS Regulatory Status

- Products
 - Investigational
 - Marketed
- Operations
 - Manufacturing
 - Marketing/Promotion
 - Distribution
- Lifecycle management status
- Pricing/Reimbursement

Assessing the Target's FDA Regulatory Status - Investigational Products

- Review status of preclinical studies, phase I, II or III studies, and pending marketing applications
 - Review recent public statements by the target
 - Review IND documents and/or pending marketing applications (NDA/BLA)
 - IRB approval requirements
 - IND reporting obligations
 - Informed consents
 - Protocol amendments/Special Protocol Assessments
 - FDA correspondence/meeting minutes

Assessing the Target's FDA Regulatory Status - Investigational Products

- Compliance
 - Care and Use of Laboratory Animals regulations
 - Good Laboratory Practices (GLPs) regulations
 - Good Clinical Practices (GCPs) regulations
 - Clinical holds/studies halted voluntarily/recalls
 - Auditing of records by FDA
 - Foreign trials
 - Clinical monitoring
 - Posting of results on clinicaltrials.gov
 - Inspections of CRO or clinical site/investigator
 - Financial disclosure
 - No debarred individuals/entities
 - Pre-approval promotion

FDA Regulatory Due Diligence - Product Development Risk Assessment

Risk spectrum for activities during product development

Lower Risk



Medium Risk



High Risk



<u>Phase I & II</u>	<u>Phase III</u>	<u>NDA Pending</u>	<u>Post Market</u>
<ul style="list-style-type: none"> • Scientific Exhibits • Press Releases • Unsolicited Requests for Information • Investigator Recruitment 	<ul style="list-style-type: none"> • Investigator Recruitment • Exhibits/congresses • Design Awareness w/HCPs • Panels of Scientific/Medical Experts /KOL development • Scientific Advisory Boards • Unsolicited Requests for Information • IR communications • Press Responses 	<ul style="list-style-type: none"> • Exhibits/congresses • Disease Awareness w/HCPs & consumers • Scientific Advisory Boards • Pre-approval Promotion • Press Briefings/Interviews • IR communications • Patient Advocacy Group communications • IIS • Regional KOL development 	<ul style="list-style-type: none"> • Reps' Details/Promotion • Unsolicited Requests for Information • Exhibits/congresses • MSL interactions with HCPs • Disease Awareness • Speaker Bureaus • Patient Advocacy Groups • Community Outreach • IIS discussions/requests

Assessing the Target's FDA Regulatory Status - Marketed Products

- Review of scope of approval or other regulatory basis for marketing
 - Determine basis of marketing (NDA, BLA, OTC monograph, grandfather status)
 - Review any Drug Master Files (DMFs)
- Scope of indications
 - Contraindications; limited patient population; other express limitations
- Review any REMS imposed

Assessing the Target's FDA Regulatory Status - Manufacturing Compliance

- Compliance with Good Manufacturing Practice (GMP) regulations
 - Review audits, inspection history (FD 483s), GMP manual, state licensure
- If contract manufacturing
 - Review contract, complaints, audits, master files, FDA inspections history
- Review compliance for both finished pharmaceuticals and active pharmaceutical ingredients (APIs)
- Review manufacturing costs/API availability
- Review adverse experience reports (AERs), pharmacovigilance data, complaints, FDA “patient advisories” on safety

Assessing the Target's FDA Regulatory Status - Distribution Compliance

- Compliance with Prescription Drug Marketing Act (PDMA)
- Review FDA inspection/compliance history
- Review compliance with state licensure requirements for distribution facilities
- Review any potential compliance issues relating to Health Information Technology for Economic and Clinical Health Act (HITECH Act) concerning privacy/security requirements under HIPAA to extent manufacturers or their partners create, receive, or transmit individually identifiable personal health information
- Controlled substances
 - Review Drug Enforcement Administration (DEA) compliance

Assessing Target's FDA Regulatory Status - Marketing Applications

- Status of all pending and approved U.S. and foreign marketing applications (NDAs/BLAs/505(b)(2))
- Review Establishment Registration and Drug Listing status
- Prescription Drug User Fee Act payments
- Annual Reports

Assessing the Target's FDA Regulatory Status - Marketing/Promotion Compliance

- Compliance with FDA marketing requirements
 - Promotion consistent with indications
 - Review of sales/marketing materials
 - Review detail force/MSLs training materials
- Review FDA Warning Letters/untitled letters and other compliance actions
- Review direct-to-consumer (DTC) promotion
- Review off-label information dissemination

Evaluating the Target's Healthcare Marketing / Promotion Compliance

- Review compliance with healthcare pricing, marketing, and distribution
 - *OIG, Compliance Program Guidance for Pharmaceutical Manufacturers*
 - *Pharmaceutical Research and Manufacturers of America (PhRMA), Code on Interactions with Healthcare Professionals*
 - *AdvaMed Code of Ethics on Interactions with Healthcare Professionals*
 - *PhRMA Guiding Principles on DTC Advertising*
 - *AMA Guidance on Interactions with Pharmaceutical Industry Representatives*
 - *ACCME Standards for Commercial Support*

Assessing the Target's FDA/CMS Marketing/Distribution Regulatory Status - Healthcare Reform Law Transparency Requirements

- Section 6002 – Physician Payment Sunshine provisions require reporting by drug, biologics, device, and medical supply companies of payments to hospitals and physicians
 - Applies to values of \$10 or more or \$100 in aggregate payments per year for reimbursable products
 - Exempts certain previously enacted state physician payment reporting laws
- Section 6001 – transparency requirements for nursing homes, physicians, and PBMs
- Requires ensuring that the target has payment tracking program in place
- Transparency requirements may provide another basis for fraud and abuse investigations

Assessing the Target's FDA/CMS Marketing/Distribution Regulatory Status - Mandatory Compliance Programs Requirement

- Healthcare Reform Law for the first time mandates that suppliers, providers, and physicians adopt a compliance and ethics program
 - CMS will issue the mandatory compliance program requirements on a rolling basis among these industry sectors
 - Likely to track the OIG guidance document
 - States are required to extend the mandatory compliance programs requirement to Medicaid
- Requirements present new opportunity for regulatory investigations as well as potential False Claims Act liability for failure to prevent or identify improper claims or payments

Assessing the Target's FDA/CMS Regulatory Compliance - Healthcare Reform Law Fraud and Abuse Program Integrity Provisions

- Healthcare Reform Law contains over 30 provisions related to healthcare fraud and abuse and program integrity, e.g.:
 - Anti-Kickback Statute is amended to relax the specific intent requirement and to provide that a violation of the statute constitutes a false or fraudulent claim under the False Claims Act
 - Section 6402 provides that identified overpayments must be reported and returned within 60 days to the applicable government contractor, intermediary, or carrier
 - Any delay in processing known overpayments creates the potential for False Claims Act liability
- Consequently, changes in fraud and abuse provisions create additional risks of government investigations and litigation

Evaluating the Target's Lifecycle Management

- Review patent status
- Review patent term extension status (potential up to 5 years)
- Review any 5-year market exclusivity for new chemical entities (NCEs) under Hatch-Waxman Amendments
- Review any 3-year market exclusivity for new indications/applications under Hatch-Waxman Amendments (e.g., Rx-to-OTC use)
- Review biosimilars patent and exclusivity status

Evaluating the Target's Lifecycle Management

- Review orphan drug exclusivity (7 years)
- Review pediatric exclusivity (6 months)
- Review generic drug exclusivity (180 days)
- Review authorized generics
- Review product extension filings (new dosages/indications/routes of administration)
- Review follow-on products (e.g., Clarinex/Claritin; Prilosec/Nexium)
- Review Rx-to-OTC use applications

Evaluating the Target's Lifecycle Management

- Assess potential economic impact of any NDAs, BLAs, 505(b)(2) applications or ANDAs filed by others
- Review any FTC/private actions regarding the target's lifecycle management activities
- Review any corporate integrity agreements affecting lifecycle management
- Review any proposals by the Independent Payment Advisory Board (IPAB) created by the Healthcare Reform Law to reduce costs for products or services for the Medicare program

Evaluating the Target's Lifecycle Management - Biosimilars

- Healthcare Reform Law establishes a new regulatory approval pathway for biosimilars
 - Provides for approval of biological products as biosimilar or interchangeable
 - Provides that there be no “clinically meaningful differences” with the pioneer biologic product
 - FDA is granted substantial flexibility in determining approval standards for biosimilars, including whether and what type of clinical studies will be required and what differences in approval process from the BLA process are appropriate

Evaluating the Target's Lifecycle Management - Biosimilars

- Grants 12 years of data exclusivity to pioneer manufacturers
 - 12 year exclusivity determined from “the date on which the reference product was first licensed”
 - An application cannot be submitted to FDA for 4 years after the date on which the BLA for the reference product was first granted
 - Supplemental BLAs are not included in the exclusivity period and do not extend it
- Approval requirements are to be set by FDA, but should include, unless FDA waives them, the following:
 - Analytical studies demonstrating the biosimilar is highly similar to the reference product
 - Animal studies
 - A clinical study sufficient to demonstrate safety, purity, and potency
 - Other information showing that the biosimilar uses the same mechanism of action, route of administration, dosage form, and strength

Evaluating the Target's Lifecycle Management - Biosimilars

- Exclusivity periods are provided for the first approved biosimilar
- Patent challenge provisions are significantly different from those under Hatch-Waxman for generic drugs
- REMS requirements are mandated to apply to biosimilars as they do to the reference pioneer biologic
- Reimbursement for biosimilars is set at ASP plus 6% of the amount determined for the reference pioneer biologic

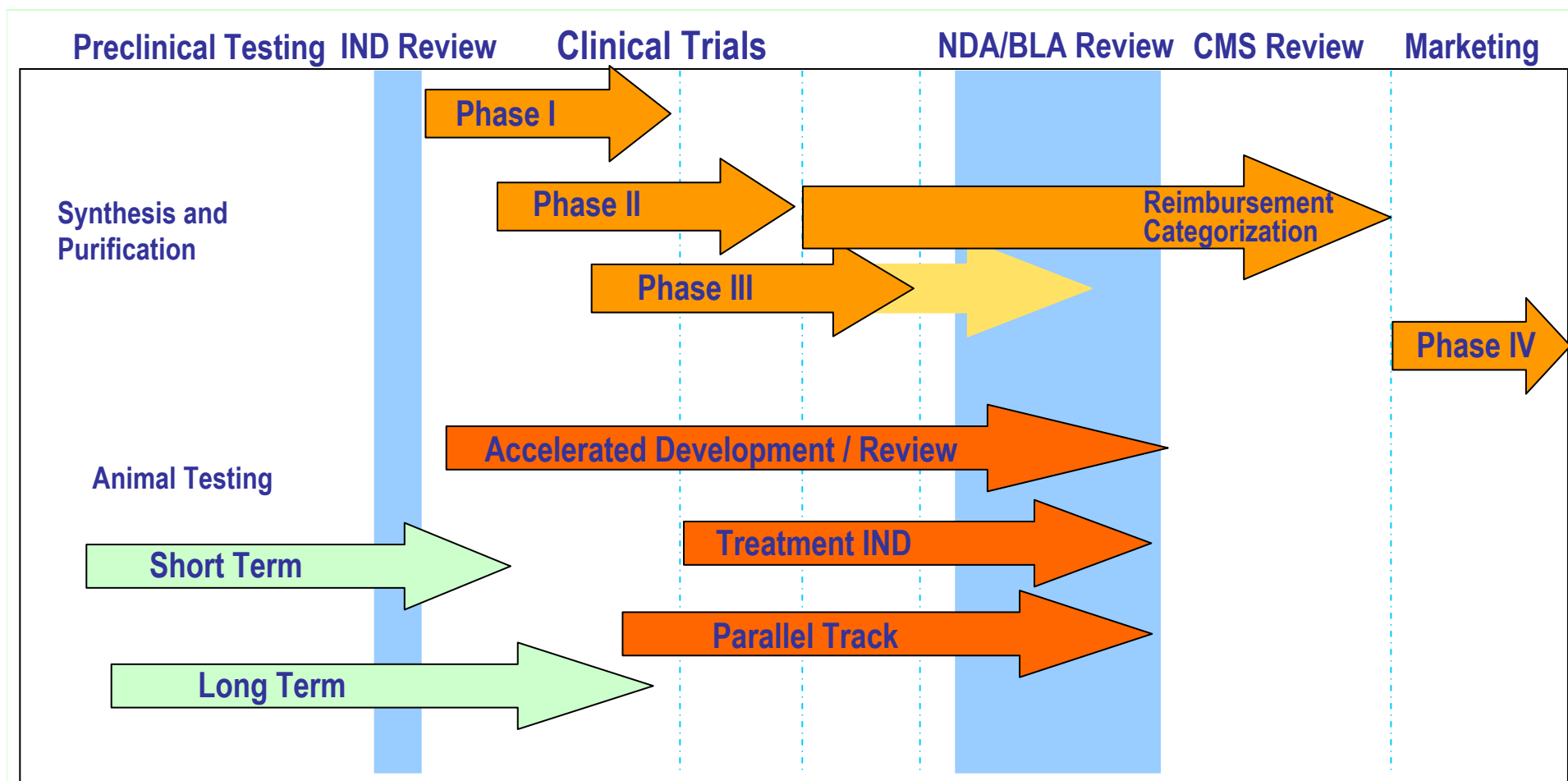
Evaluating the Target's Lifecycle Management - Biosimilars

- Significant uncertainty under the new provisions in view of the substantial discretion provided to FDA regarding details and standards for submissions and approvals of biosimilars
 - See Congressional Research Service, *FDA Regulation of Follow-On Biologics* (April 26, 2010), describing the scientific challenges for FDA in approving biosimilars
 - See Federal Trade Commission, *Emerging Health Care Issues: Follow-on Biologic Drug Competition* (June 10, 2009), providing an analysis of the likely nature of competition in a biosimilars market and the significant differences likely with the competitive dynamics of the generic drugs market

Evaluating the Target's Healthcare Reimbursement Status

- Review product's reimbursement status under Medicare, Medicaid, and private healthcare insurer programs
- Review history of interactions with Centers for Medicare and Medicaid Services (CMS)
 - Review any discussions by the target at investigational stage with CMS on therapeutic reimbursement category and coverage of the product

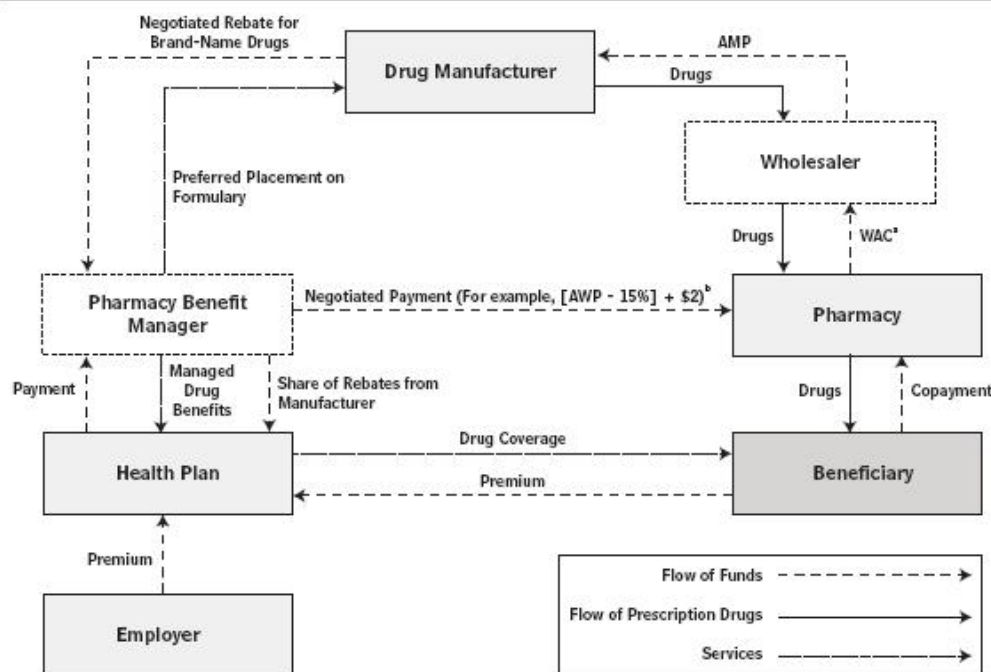
Evaluating the Target's Healthcare Reimbursement Status - Timing



Evaluating the Target's Healthcare Reimbursement Status

Example:

Flow of Funds for Single-Source Brand-Name Drugs Purchased at a Retail Pharmacy and Managed by a Pharmacy Benefit Manager for an Employer's Health Plan



Source: Congressional Budget Office.

Note: AMP = average manufacturer price; WAC = wholesale acquisition cost; AWP = average wholesale price.

a. The WAC is a list price that approximates what conventional pharmacies pay wholesalers for single-source brand-name drugs.

b. Based on Novartis Pharmaceuticals Corporation, *Pharmacy Benefit Report: Facts & Figures* (2004), p. 16.

Evaluating the Target's Healthcare Reimbursement Status - Comparative Effectiveness Research

- Healthcare Reform Law contains provisions supporting the development of comparative effectiveness research (CER) concerning healthcare products and services
- Section 6301 establishes the Patient-Centered Outcome Research Institute to assist in conducting CER and disseminating research findings
 - The Institute is to identify national priorities, establish a methodology committee, and establish a research project agenda
- The Institute is required to ensure that CER “findings not be construed as mandates for practice guidelines, coverage recommendations, payment, or policy recommendations”
 - Private payers can use such findings as a basis for their product or service approval or reimbursement decisions
 - Note that Wellpoint plans to issue updated criteria on how to submit CER data to its pharmacy and therapeutics committee. ([Pink Sheet](#), April 19, 2010)
- Potential for controversy - note rejection of 2009 recommendations by U.S. Preventive Services Task Force to end routine mammograms for women in their forties

Evaluating the Target's Healthcare Reimbursement Status - Comparative Effectiveness Research

- Healthcare Reform Law allows CMS to use CER results to make a determination concerning Medicare coverage if such use is through an iterative and transparent process and a determination to deny coverage is not based solely on CER
 - Note that the Agency for Healthcare Research and Quality is considering use of “academic detailing” to disseminate CER to healthcare providers ([Pink Sheet](#), April 26, 2010)
- Significant practical limitations on use of CER including absence of accepted protocols, lack of historical CER studies for comparison, and controversy as to interpretation of results

Evaluating the Target's Healthcare Reimbursement Status - Comparative Effectiveness Research

- Assess whether comparative effectiveness or cost effectiveness trials are components of target's clinical trials
 - Increasing importance of inclusion of pharmacoeconomics considerations at clinical trials stage
 - First comparative effectiveness trial of two pioneer drugs by National Institutes of Health currently being conducted
 - Comparative trial of two Genentech drugs (Lucentis - \$2,000/dose and Avastin - \$40/dose)
- Review any assessments by the U.K.'s National Institute for Healthcare and Clinical Excellence
 - NICE recently denied use by the National Health Service of two leukemia products, Sprycel and Tassigna, on the basis of clinical effectiveness and cost concerns (Pink Sheet, Feb. 15, 2010)

Consequences of Healthcare Reform Law for M&A / Partnering

- Healthcare Reform Law presents significant challenges for effective valuation of target products or companies
 - Potential for restrictions on Medicare or Medicaid coverage and reimbursement from comparative effectiveness research
 - Potential for adoption of mirror restrictions on coverage and reimbursement by private payers
 - Potential for approval of biosimilars
 - Potential for expanded fraud and abuse investigations and litigation
 - Potential for adverse impacts on product suppliers from value-based purchasing and other requirements imposed on providers by the Healthcare Reform Law
- Need to closely monitor FDA and CMS development of regulations and administrative application of Healthcare Reform Law as to potential effects on product or company acquisition valuations.

Environment Affecting Service Providers

- Due diligence for life sciences companies (product manufacturers) should include review of current environment for healthcare service providers (i.e., buyers of prescription drugs, devices, biologics)
- Healthcare Reform Law represents major event for most healthcare providers
- Important to evaluate short-term, mid-term, and long-term trends and changes
- Nature of impact still evolving and will continue to evolve over course of Law's implementation
- Many aspects of impact may change over time

Environment Affecting Service Providers

Topics to include in review

- Will Healthcare Reform significantly impact payor mix for providers? Reduce number of uninsured? When?
- Who are the newly covered? What will they be covered for (new benefits packages)?
- How will an increase in insured affect private insurers' relationships with providers?
- Medicare provider payment changes
- Quality requirements and impact on providers
- Medical necessity determinations/comparative effectiveness
- Compliance/enforcement environment

Coverage Increases – Impact on Healthcare Providers?

Individual insureds

- Mandate begins in 2014, penalty through income tax if not covered
- Premium subsidies on sliding scale for 133%-400% of Federal Poverty Level (FPL)
- New individuals will access coverage mainly through state-operated exchanges
- Individuals will enroll in “qualified” private plans with “essential health benefit” packages
- Some exchange requirements will affect plan/provider relationships (*e.g.*, out of network providers)

Coverage Increases – Impact on Healthcare Providers?

Employer requirements

- Immediate/near-term employee benefit changes (e.g., dependent coverage)
- Most employer requirements begin in 2014
- Pay (penalty) or play (offer coverage) or both
- Small employer exceptions to penalty structure
- Small employer access to state-operated exchanges

Coverage Increases – Impact on Healthcare Providers?

Medicaid

- Medicaid eligibility streamlining - add predictability for providers? Decrease administrative costs? Increase number of Medicaid patients?
- Medicaid expansion
 - Up to 133% of Federal Poverty Level
 - All individuals under age 65
 - Benchmark benefit package (at least essential health benefits)
 - Limited provider payment relief (primary care)

Coverage Increases – Impact on Healthcare Providers?

Interaction of expanded coverage

- Expansion of Medicaid - new coverage or replacement coverage? Or both?
- Expansion of coverage through exchanges - new coverage or replacement coverage? Or both?
- Coverage changes likely to have biggest impact on providers with high % of uninsured patients
- Near term DSH payment decreases

Coverage Increases – Impact on Healthcare Providers?

Benefits

- What will newly insured be covered for?
- Defined benefits - “essential health benefits package” for “qualified” health plans statutory list with HHS implementation
- Broad statutory list positive for most providers
- Statutory list includes Rx drugs

Coverage Increases – Impact on Healthcare Providers?

Provider/Payor relationships

- How to analyze the impact of coverage changes on provider/payor relationships?
- Which private payors will continue in or enter Medicaid market (Medicaid managed care)?
- Which private payors will opt to participate in exchange coverage? Which payors have relevant experience for this newly regulated market?
- Significant overlap and/or consolidation of payors in Medicaid and exchange markets?
- Post 2014 analysis very speculative

Medicare Provider Payment Changes

Impact on Hospitals

- Increased financial pressure on hospitals as a result of multiple payment changes in Healthcare Reform Law
- Payment constraints and incentives
 - Market basket (MB) update for IPPS and OPPS hospitals subject to cuts beginning FY/CY 2010
 - Productivity adjustment to be applied to MB update for IPPS and OPPS hospitals beginning FY/CY 2012
 - Medicare DSH payments reduced 75% beginning in FY 2014

Medicare Provider Payment Changes

Impact on Hospitals (con't)

- Payment changes (budget neutral) based on VBP performance standards beginning FY 2013
- 1% payment reduction to IPPS hospitals in top quartile for HACs beginning FY 2015
- Payment adjustments for high hospital readmission rates beginning in FY 2013
- Changes to GME payments for academic medical centers beginning July 1, 2011
- How will these payment cuts offset the expected improved payor mix?

Medicare Provider Payment Changes

Physician and other providers

- Physicians - Still no long term Medicare
- Physician Fee Schedule reform
- VBP for other providers
- Payment cuts to most Medicare providers

Medicare Provider Payment Changes

Independent Payment Advisory Board (IPAB)

- New 15-member IPAB that will present Congress with proposals to reduce costs and improve quality for entire Medicare program
- May address both products and services
- IPAB cannot make proposals to ration care, raise taxes or Part B premiums, or change Medicare benefit, eligibility, or cost-sharing standards

Quality Requirements – Impact on Healthcare Providers?

- Current trend of payor quality requirements accelerates in Healthcare Reform Law
- Growing intersection between quality requirements and payment amounts
- Development of near-term Medicare Value-Based Payment (VBP) modifiers for physicians and other providers
- Establishment of hospital VBP program with payment modified based on quality performance

Quality Requirements – Impact on Healthcare Providers?

- Public performance reporting of quality and resource use measures
- Impact of VBP and quality expectations on provider purchasing trends?
- Center for Medicare and Medicaid Innovation and other pilot and demonstration projects
- Overall national quality improvement strategy - HHS, the Agency for Healthcare Research and Quality, and CMS must identify gaps and needed improvement

Medical Necessity and Comparative Effectiveness

Medical necessity for providers/products/services

- Current trend for tougher medical necessity/coverage requirements in Medicare
- Scrutiny of provider ordering of items and services (e.g., “in-person” evaluation for DME)
- Expediting this trend through Healthcare Reform Law’s addition of comparative effectiveness research and review

Compliance / Enforcement Environment for Providers

Compliance review

- Compliance review always important in due diligence, even more important now
- HHS to develop mandatory compliance program requirements
- Healthcare Reform Law toughens procedures for Medicare/Medicaid/CHIP provider/supplier screening
- Implications of compliance issues for operations (e.g., quality/payment intersection, transparency requirements prompting tracking)

Compliance / Enforcement Environment for Providers

Enforcement environment

- Multiple fraud and abuse and “program integrity” provisions
- Increased funding and penalties for fraud and abuse violations
- Tough overpayment reporting requirements
- Intersection between provider compliance requirements and behavioral changes that emerge from compliance environment that could affect provider/manufacturer relationships

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